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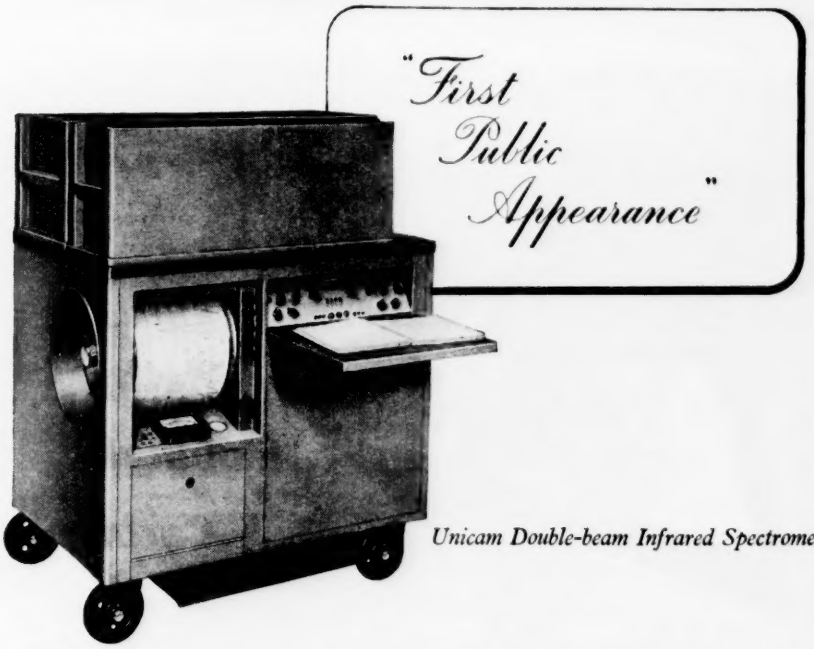

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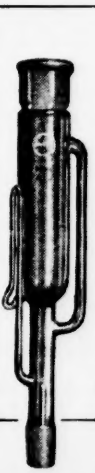

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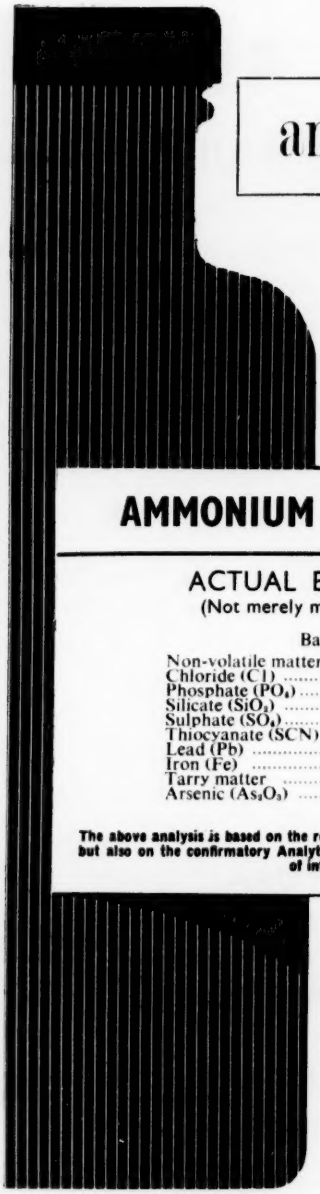

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Phosphate (PO_4)	0·0005%
Silicate (SiO_3)	0·0002%
Sulphate (SO_4)	0·0014%
Thiocyanate (SCN)	0·00004%
Lead (Pb)	0·00005%
Iron (Fe)	0·00002%
Tarry matter	No Reaction
Arsenic (As_2O_3)	No Reaction

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211. *Kinetics of the Reaction of Potassium Ferrocyanide and Nitrosobenzene: the Catalytic Action of Mercuric Ions and Ultra-violet Light.*

By S. Ašperger, I. Murati, and O. Čupahin.

The kinetics of the reaction of potassium ferrocyanide with nitrosobenzene in aqueous solution were studied spectrophotometrically by measuring the extinction of the violet complex ion $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$. The absorption spectrum of its solution was determined. The solutions follow the Beer–Lambert law. The approximate value of the activation energy for the reaction $Fe(CN)_6^{4-} \xrightarrow{H_2O} Fe(CN)_5.H_2O^{3-} + CN^-$ was calculated as 19·8 kcal./mole.

Mercuric ions accelerate the reaction very strongly, even at a concentration of 10^{-7}M. This action is specific for mercuric ions and could be utilised for the determination of traces of Hg^{++} in distilled water. In the presence of mercuric ions the reaction shows a negative salt effect.

The action of ultra-violet light leads to the same reaction product as the action of Hg^{++}. The kinetics of the process in ultra-violet light was studied photoelectrically. Mercuric ions accelerate the process in the light very considerably. Cyanide ions suppress the reaction. The reaction mechanism is discussed.

Previous investigations of the decomposition velocity of aqueous solutions of potassium ferrocyanide in ultra-violet light (Ašperger, *Trans. Faraday Soc.*, 1952, **48**, 617) confirmed the reaction mechanism proposed by Baudisch (*Ber.*, 1929, **62**, 2706) and Iimori (*Z. anorg. Chem.*, 1927, **167**, 157); small quantities of $Fe(CN)_5.H_2O^{3-}$ arise in the first phase of decomposition. Its absorption does not differ much from that of the ferrocyanide ion, so it is difficult to observe small quantities of $Fe(CN)_5.H_2O^{3-}$ directly in excess of ferrocyanide. But since pentacyanides give coloured complexes with aromatic nitroso-compounds (Baudisch, *loc. cit.*) the decomposition of aqueous ferrocyanide solutions can be studied by adding nitrosobenzene, for instance. In this case, according to earlier investigations, the following reaction mechanism can be supposed:

$$Fe(CN)_6^{4-} \overset{H_2O}{\rightleftharpoons} Fe(CN)_5.H_2O^{3-} + CN^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Fe(CN)_5.H_2O^{3-} + C_6H_5{\cdot}NO \xrightarrow{\text{violet}} Fe(CN)_5.C_6H_5{\cdot}NO^{3-} + H_2O \quad . \quad . \quad . \quad . \quad (2)$$

$$CN^- + H_2O \rightleftharpoons HCN + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The equilibrium of reaction (1), in the dark, is shifted almost completely towards the left; but if we prevent the reaction between $Fe(CN)_5.H_2O^{3-}$ and CN^- by inducing the relatively fast irreversible process (2) we can measure the velocity of decomposition of ferrocyanide into aquopentacyanide. This process has not yet been studied. The decomposition of ferrocyanide into pentacyanide, being very slow, controls the velocity of the whole process, which was followed by measuring the extinction of the violet complex.

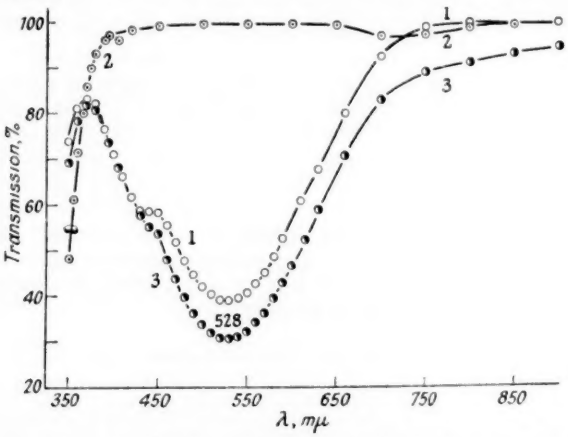
Experimental

Materials.—Nitrosobenzene was prepared according to Bamberger (*Ber.*, 1894, **27**, 1555). A stock solution was made by dissolving 0·666 g. in 1 l. of distilled water at 70°. The light green solution is stable for a few days; then it becomes turbid and cannot be used. The molar concentrations given always relate to the monomeric form. Potassium ferrocyanide trihydrate was Merck's analytical grade.

Stability of Aqueous Solutions of Potassium Ferrocyanide.—The pH of a freshly prepared 0·1M-solution increased from 6·42 to 7·70 during 4 days in a closed vessel in the dark, and became constant at *ca.* 8 after 15 days. The measurements are not readily reproducible, although an increase in pH is always found. This change is probably due to reactions (1) and (3). The measurements were performed by a glass electrode on a Doran pH Meter M. 4981. The same instrument was used for all further pH measurements.

Absorption Spectrum of $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$.—An aqueous solution of potassium ferrocyanide ($5{\cdot}0 \times 10^{-2}$M) and nitrosobenzene ($5{\cdot}2 \times 10^{-5}$M) was exposed to ultra-violet light for about 5 hours. The ultra-violet light accelerates the otherwise very slow process. After termination of the reaction, which is irreversible, the violet solution had almost the unchanged initial concentration of potassium ferrocyanide, and approximately 5×10^{-5}M-$Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$. The absorption spectrum of the violet solution was measured by means of the Unicam S.P. 500 Quartz Spectrophotometer; a $5{\cdot}0 \times 10^{-2}$M-solution of potassium ferrocyanide was taken as a standard. The absorption maximum is situated at 528 mμ (Fig. 1, curve 1). Unused nitrosobenzene cannot impair the measurements since it scarcely absorbs in the visible region, as shown by curve 2, Fig. 1. All the subsequent spectrophotometric measurements were made at 528 mμ, *i.e.*, at the maximum of absorption. The violet solutions of $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$ obey the Beer–Lambert law. The mixture of 0·10M-ferrocyanide and approximately 6×10^{-4}M-nitrosobenzene was exposed to ultra-violet light for several hours. The extinction was measured against 0·10M-$K_4Fe(CN)_6$ standard. The solution was then repeatedly diluted with the standard solution, and the extinction measured. A linear dependence between extinction and concentration of $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$ was established; the

FIG. 1. *Transmission curves*: (1) $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$, ca. 5×10^{-5}M, *obtained by action of ultra-violet light on a solution containing* $5{\cdot}0 \times 10^{-2}$M-$K_4Fe(CN)_6$ *and* $5{\cdot}2 \times 10^{-5}$M-*nitrosobenzene*; (2) *nitrosobenzene*, $4{\cdot}2 \times 10^{-4}$M, *in distilled water*; (3) $Fe(CN)_5.C_6H_5{\cdot}NO^{3-}$, ca. 5×10^{-5}M, *obtained by action of* Hg^{++} *on a solution containing* $5{\cdot}0 \times 10^{-3}$M-$K_4Fe(CN)_6$ *and* $5{\cdot}2 \times 10^{-5}$M-*nitrosobenzene*. *Thickness of layer* = 1 *cm*.



same linear dependence was obtained even when the dilution was carried out with distilled water (Fig. 2). This shows, at the same time, that the absorption of potassium ferrocyanide at 528 mμ and under the above conditions is so small that it may be neglected.

Velocity of Reaction of Potassium Ferrocyanide with Nitrosobenzene in the Dark.—A mixture of freshly prepared aqueous solutions of ferrocyanide and nitrosobenzene was kept in a water thermostat (±0·05°) in the dark. Samples were taken at definite reaction times in faint yellow light, and the extinction of the violet product measured; the standard was a solution of potassium ferrocyanide of the same concentration as in the original solution. It was found that the initial reaction velocity (= extinction in the tenth minute) depends on the concentration of potassium ferrocyanide, which was varied from $5{\cdot}0 \times 10^{-4}$M, at which the reaction is scarcely perceptible, up to $5{\cdot}0 \times 10^{-1}$M, where, after 100 minutes, distinctly violet solutions were obtained. The temperature and the initial concentration of nitrosobenzene (20°; $4{\cdot}2 \times 10^{-4}$M) were kept constant. The initial velocity also depends on the concentration of nitrosobenzene, but only up to *ca.* $1{\cdot}4 \times 10^{-3}$M; then the dependence rapidly disappears, because reaction (1) takes over control of the velocity of the total process.

Influence of temperature. With $5{\cdot}0 \times 10^{-4}$M-potassium ferrocyanide and $4{\cdot}7 \times 10^{-3}$M-nitrosobenzene, reaction is still perceptible at 20°. At a definite reaction time several ml. of solution were withdrawn and poured into a dry vessel, cooled below 0°; the solution was thus rapidly cooled to about 5°, at which temperature the reaction practically stops, and the extinction was measured. A standard solution identical in composition with the original

reaction mixture was freshly prepared every 30 minutes and kept constantly at 5°. The results of the measurements with freshly prepared ferrocyanide solutions are shown in Fig. 3.

If we plot logarithms of the extinctions measured in the tenth minute ($\log_{10} E_{10}$) against $1/T$, we obtain a straight line, whose slope corresponds to an activation energy of 19·8 kcal./mole (Fig. 4). This value is only approximately that of the activation energy of the slowest process (1). The velocity constants could not be determined since the violet complex slowly decomposes at a higher temperature; this can be neglected initially, but becomes considerable during the course of a long run.

Measurements analogous to those of Fig. 3 were carried out with ferrocyanide solutions 3—4 days old. The velocity of reaction with old ferrocyanide solutions is always somewhat smaller, but the activation energy is approximately the same as reported above.

Catalytic Action of Mercuric Ions on Velocity of Reaction.—The catalytic action of mercuric ions on the decomposition of aqueous potassium ferrocyanide in acid solution, and the accelerated production of Prussian-blue, was described by Pinter [*Farm. Vjesnik*, 1940, 3 (Zagreb, Croatia)]. We added a small quantity of very dilute mercuric chloride solution to a weakly acid, neutral, or weakly alkaline mixture of aqueous solutions of potassium ferrocyanide and nitrosobenzene, and observed that the violet complex was formed very quickly.

The violet compound, obtained by action of ultra-violet light or by action of mercuric ions in the dark, has the same absorption spectrum in both cases. This was shown as follows. Reaction in a solution of $5{\cdot}0 \times 10^{-3}$M-$K_4Fe(CN)_6$, $5{\cdot}0 \times 10^{-5}$M-$C_6H_5{\cdot}NO$ and $5{\cdot}0 \times 10^{-4}$M-$HgCl_2$ was generally complete after 15 hours, and then the absorption spectrum of the violet complex, of concentration approximately equivalent to that of the original nitrosobenzene, was determined; a solution of ferrocyanide of the same concentration as in the reaction mixture was taken as a standard. Curve 3, Fig. 1, was obtained, and it is analogous to curve 1, Fig. 1, where the violet compound was produced by the action of ultra-violet light, in absence of mercuric ions.

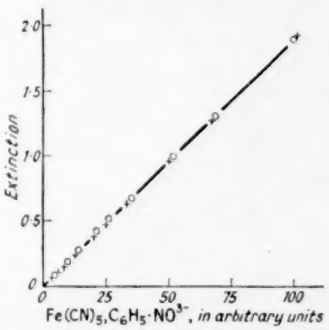


FIG. 2. *Dependence of the extinction* ($\lambda = 528$ mμ) *on the concentration of* $Fe(CN)_5{\cdot}C_6H_5NO^{3-}$: ×, *dilution with* 0·10M-$K_4Fe(CN)_6$; o, *dilution with* H_2O. *Thickness of layer* = 1 *cm.*

The velocity of reaction of potassium ferrocyanide and nitrosobenzene in presence of mercuric ions depends on pH, being a maximum at pH 3·5 (Fig. 5). The pH required was produced by addition of a few drops of sodium hydroxide or of hydrochloric acid to a mixture of nitrosobenzene and mercuric chloride solutions; the solution of ferrocyanide was brought to the same pH. The reaction solutions were separately placed in the thermostat at 20° in the dark, and after they had acquired this temperature they were mixed. After 30 minutes, the extinction E_{30} was measured against a standard of freshly prepared potassium ferrocyanide and nitrosobenzene solutions of the same concentrations as in the original reaction mixture. The foregoing measurements showed that the extinction of the standard solution does not change in these circumstances. (Extremely dilute solutions of mercuric chloride must be prepared just before use, since the salt is slowly adsorbed on glass.)

Since the catalytic action of Hg^{++} is a maximum at pH 3·5, we examined the dependence of the reaction velocity on the concentration of Hg^{++} at this pH. The concentrations of potassium ferrocyanide and nitrosobenzene being kept constant at $5{\cdot}0 \times 10^{-4}$ and $4{\cdot}2 \times 10^{-4}$M, respectively, the concentration of mercuric chloride was varied from 10^{-7}M to 10^{-4}M. After a reaction time of 30 minutes (at 20°), the extinction E_{30} was measured. The results are shown in Fig. 6. It is evident that the catalytic action of Hg^{++} is so large that it can be observed even at the concentration of 10^{-7}M, for at this concentration the absorption in a 1-cm. layer, measured in the 30th minute (A_{30}) was 1·3%. At 5×10^{-7}M-mercuric chloride the violet colour of the

complex is distinctly visible. On the basis of the catalytic action of mercuric ions on the reaction, a method for the determination of traces of mercuric ions in distilled water was developed. The catalytic action is strictly specific for mercuric ions. Other metal cations do not interfere with this reaction unless they cause a turbidity. $AgNO_3$, $SnCl_2$, and $CdSO_4$ in concentration less than 10^{-4}M did not produce any turbidity; $Pb(NO_3)_2$ and $ZnCl_2$ gave a slight, constant turbidity at 10^{-4}M, but were dissolved clearly at 10^{-5}M. 10^{-5}M-$CuCl_2$ gives a clear, slightly reddish-brown solution of cupric ferrocyanide which causes a constant absorption of 1·4% at 528 mμ and $d = 1$ cm.

The reaction of ferrocyanide and nitrosobenzene in presence of mercuric ions shows a negative salt effect. Addition of 0·7M-KNO_3 reduces the extinction E_{30} by 41% at concentrations

FIG. 3. *Dependence of the velocity of reaction in the dark on temperature:* $K_4Fe(CN)_6$ $5·0 \times 10^{-4}$M; *nitrosobenzene* $4·7 \times 10^{-3}$M.

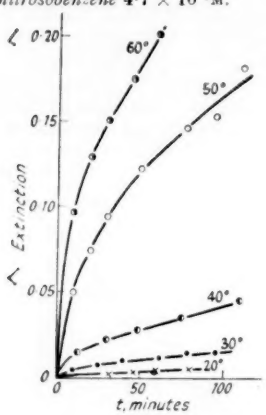


FIG. 4. *Influence of temperature on the reaction in the dark.*

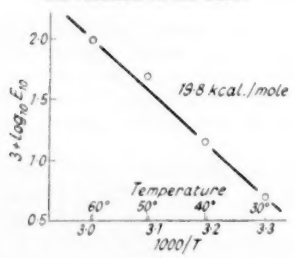


FIG. 5. *Dependence of velocity of reaction in presence of mercuric ions on* pH. E_{30} = *extinction in the* 30*th minute at* 528 mμ; $5·0 \times 10^{-4}$M-$K_4Fe(CN)_6$; $4·2 \times 10^{-4}$M-C_6H_5·NO; $6·66 \times 10^{-6}$M-$HgCl_2$, 20°.

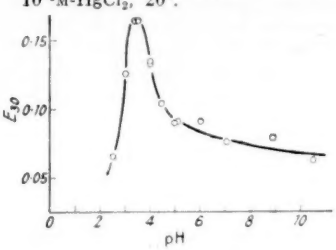
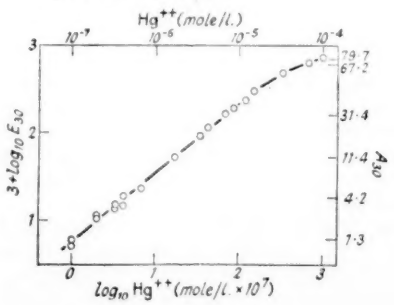


FIG. 6. *Dependence of extinction and absorption in the* 30*th minute* (E_{30} *and* A_{30}) *on the concentration of* Hg^{++}: $5·0 \times 10^{-4}$M-$K_4Fe(CN)_6$; $4·2 \times 10^{-4}$M-C_6H_5·NO; pH = 3·5; $t = 20°$; $\lambda = 528$ mμ.



$K_4Fe(CN)_6$ $5·0 \times 10^{-4}$M, C_6H_5·NO $4·2 \times 10^{-4}$M, and $HgCl_2$ $6·66 \times 10^{-4}$M. This is in agreement with Brönsted's theory, since the charges of ferrocyanide and mercuric ions are of opposite signs.

Velocity of Reaction in Ultra-violet Light.—Apparatus. A glass cell (5 × 5 × 1 cm.) containing the mixture of aqueous solutions of potassium ferrocyanide and nitrosobenzene was placed in an air-thermostat (±0·3°). The solution was stirred vigorously. A Philips Philora lamp HO 2000 was used as a source of light. A second glass cell, containing distilled water, served as a thermal filter. Close behind the reaction vessel, screened by an orange filter OG2, Schott und Gen., Jena, there was a selenium photo-element. The extinctions were measured by means of a Lange reflection galvanometer.

Photoactive light. Our earlier investigations (*loc. cit.*) showed that with the above lamp the photoactive light for ferrocyanide solutions is represented by a group of lines of mean wavelength 365·5 mμ; the other Hg lines do not come into consideration as photoactive light. The violet complex ion $Fe(CN)_5C_6H_5$·NO^{3-} absorbs the photoactive light relatively weakly, because

the maximum of transmission is situated just at 370 mμ (Fig. 1, curves 1 and 3). This absorption is particularly weak initially, when the extinctions E_{20} were read.

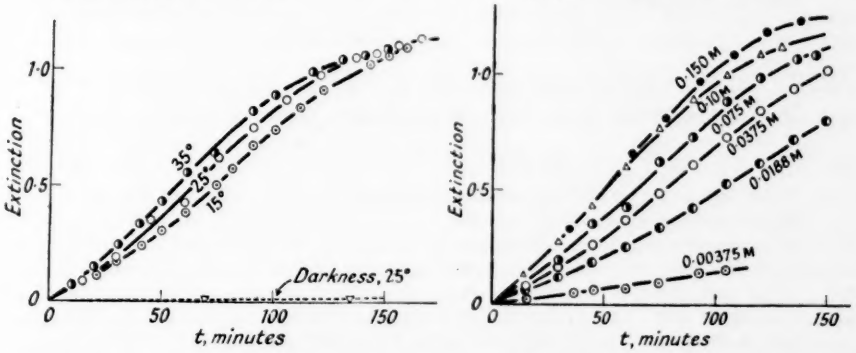
The aqueous solutions of nitrosobenzene absorb the photoactive light rather strongly (Fig. 1, curve 2). In these experiments the initial concentration of nitrosobenzene was always the same ($3{\cdot}1 \times 10^{-3}$M). At the time of measurement of E_{20}, the change in concentration of nitrosobenzene is small so that its absorption could be regarded as constant.

Light used for measurements. The OG2 filter transmitted the yellow mercury lines 579·07 and 576·96 mμ. The orange Hg lines 607·3, 612·3, and 623·4 mμ are so weak that they could not be observed spectroscopically through the filter. Nitrosobenzene and potassium ferrocyanide practically do not absorb yellow light (Fig. 1), wherefore the change in extinction is caused only by change in concentration of the violet complex.

Influence of temperature on the velocity of reaction. On the supposition that the photodecomposition of ferrocyanide into pentacyanide is the slowest process in the system (1), (2), and (3), one would expect but a slight dependence of the total reaction velocity on temperature. The velocities of reaction were measured at 15°, 25°, and 35° (Fig. 7). The mean temperature coefficient Q_{10}, determined by means of the extinctions E_{20}, is 1·2; this value is, of course, only approximate, because the velocity constants could not be determined. The value obtained for

FIG. 7. *Dependence of the velocity of reaction in light on the temperature. The velocity of reaction in the dark*: $K_4Fe(CN)_6$ $7{\cdot}50 \times 10^{-2}$M; $C_6H_5{\cdot}NO$ $3{\cdot}1 \times 10^{-3}$M.

FIG. 8. *The velocity of reaction in light at various concentrations of* $K_4Fe(CN)_6$. $C_6H_5{\cdot}NO$ $3{\cdot}1 \times 10^{-3}$M; $t = 25°$.



Q_{10} corresponds to a photo-reaction. Now, since reaction (1) is the slowest process in the irradiated system, it is certainly by far the slowest as a thermal reaction.

In Fig. 7 the velocity of reaction in the dark at 25°, with the same concentrations as in the photoreaction, is also represented (broken curve). The velocity of the reaction in the dark was measured in the following manner: the assembly for the measurement of the photoreaction, described above, was modified by transferring the OG2 filter to the front of the cell containing the reaction mixture. The light of the Philora lamp was screened off by closing the door of the thermostat. At a certain reaction time the door was opened for a short time and inactive yellow light was allowed to pass through the mixture. The extinction was measured analogously as in the case of photoreaction. It is evident from Fig. 7 that the reaction in the dark, under the specified conditions, is so slow that it can be ignored.

Dependence of velocity of reaction on concentration of $K_4Fe(CN)_6$. The dependence is represented in Fig. 8. By calculating the absorption of photoactive light (365·5 mμ), *e.g.*, for 0·0375M-$K_4Fe(CN)_6$ (molecular extinction coefficient, according to our earlier investigations, *loc. cit.*: 76·6; $d = 1$ cm.), we find the value 99·9%. From this concentration upwards, the absorption of photoactive light is practically complete; even at 0·0188M-$K_4Fe(CN)_6$ it is considerable (96·4%). We see nevertheless that the velocity of reaction in the range of total absorption depends on the concentration of $K_4Fe(CN)_6$.

The velocity of reaction also depends on the concentration of nitrosobenzene up to about 2×10^{-3}M; above that it is practically independent of this concentration.

Influence of pH. The velocity of reaction in light depends on pH, being a maximum at pH 4·7 as compared with 3·5 in the presence of mercuric ions.

Influence of foreign electrolytes. The concentrations of reactants were: $K_4Fe(CN)_6$

$7{\cdot}50 \times 10^{-2}$M; $C_6H_5{\cdot}NO$ $3{\cdot}1 \times 10^{-3}$M. 0·25M-Sodium cyanide prevented the photo-process almost completely, and $1{\cdot}2 \times 10^{-2}$M-sodium cyanide reduced the extinction E_{20} by 50%. The action of CN^- consists in the mass-action effect on the equilibrium (1) to favour ferrocyanide. Potassium cyanate had no effect upon the reaction. Mercuric chloride accelerates the process in light, a concentration of $3{\cdot}7 \times 10^{-4}$M making it almost instantaneous. Except for the ions mentioned, the velocity of reaction is mainly independent of ionic strength.

Discussion.—The dependence of the velocity of reaction on the concentration of potassium ferrocyanide in the range of total absorption indicates that the elementary photochemical act does not consist in the direct dissociation of ferrocyanide ion into pentacyanide and cyanide ions, for in such a case Bunsen and Roscoe's law would be followed and the velocity of reaction would be independent of ferrocyanide concentration. Reaction (1), as suggested in our earlier investigations (*loc. cit.*) where the same dependence was observed by a different method, seems to represent the overall equation of a more complicated process.

[*Added in proof*, 12.2.53.] A simple, quick, and sensitive method for determination of mercury vapour and mercury-bearing dust in the atmosphere has recently been developed on the basis of the catalytic action of mercuric ions, and will be reported in due course.

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212. 2-*Mercaptoglyoxalines. Part VII.* The Preparation of Di-C-substituted* 2-*Mercaptoglyoxalines from Aspartic Acid.*

By ALEXANDER LAWSON.

By the action of acid anhydrides on benzoylaspartic anhydride (I; R = Ph) two series of products are obtained by acylation and loss of carbon dioxide. One corresponds to the product obtained by Dakin and West (*J. Biol. Chem.*, 1928, **78**, 745); the other comprises azlactones of β-acylamino-γ-keto-acids (III), and these undergo hydrolysis to α-amino-ketones which may be converted into 4-alkyl-2-mercapto-5-glyoxalinylacetic acids (VII). The last named on decarboxylation give the corresponding 4 : 5-dialkyl-2-mercaptoglyoxalines.

IN Part VI * the preparation of 4 : 5-dialkyl-2-mercaptoglyoxalines from the simple amino-acids by the Dakin and West reaction (*J. Biol. Chem.*, 1928, **78**, 91) was described. In applying their reaction to dicarboxylic amino-acids, Dakin and West (*ibid.*, p. 745) again observed the production of ketonic products with evolution of carbon dioxide; in the case of aspartic acid, the non-crystalline product isolated was thought to consist largely of the acetyl derivative of β-amino-γ-ketovaleric acid (XIV) on the basis of the isolation of the hydrolytic products diacetyl and ammonium chloride, the former having been considered as arising from the breakdown of the intermediate β-hydroxylævulic acid.

The work now described arose out of the observation that acid anhydrides acylate benzoylaspartic acid and its anhydride with loss of carbon dioxide in the absence, as well as in the presence, of a basic catalyst such as pyridine. From the resulting benzamido-ketones disubstituted 2-mercaptoglyoxalines are readily obtained.

The structure of acylaspartic anhydrides has been discussed by Harington and Overhoff (*Biochem. J.*, 1933, **27**, 338) who on the basis of the isolation of the acid chloride of 2-methyl-oxazol-5-one-4-acetic acid from the reaction between acetylaspartic anhydride and phosphorus pentachloride favoured an oxazolone structure. Barker (*Nature*, 1951, **168**, 908), on the other hand, proved the true anhydride structure by isolation of two anilides from both acetyl- and benzoyl-aspartic anhydride (cf. also Swan, *Nature*, 1952, **169**, 826) and by absence of reaction with diazomethane and of racemisation in aqueous sodium

* Part VI, *J.*, 1952, 1350.

acetate. He pointed out, however, that the partial racemisation in du Vigneaud and Meyer's procedure (*J. Biol. Chem.*, 1932, **98**, 295) and complete racemisation of acetylaspartic anhydride by sodium acetate and acetic anhydride may be due to the presence of the oxazolone, possibly in equilibrium with the anhydride. Further, benzoylaspartic anhydride and ammonia give benzoyl*iso*asparagine (Pauly and Weir, *Ber.*, 1910, **43**, 665) whereas acetylglutamic anhydride for which the true anhydride structure is accepted (cf. King and MacMillan, *J. Amer. Chem. Soc.*, 1952, **74**, 2859) gives acetylglutamine.

Benzoylaspartic anhydride is obtained in quantitative yield by dissolving the acid as rapidly as possible in acetic anhydride on the steam-bath and allowing the solution to cool. When the anhydride is heated in boiling acetic anhydride it rapidly dissolves and 1 mol. of carbon dioxide is evolved. The neutral crystalline product, $C_{12}H_{11}O_3N$, m. p. 94°, is unchanged by further heating with acetic anhydride in 2-picoline, which indicates the absence of an amide-hydrogen atom. It gives an immediate precipitate of a hydrazone containing an additional 2 carbon and 6 hydrogen atoms when treated with ethanolic dinitrophenylhydrazine containing a little concentrated sulphuric acid: alcoholysis of a lactone ring seems to be involved here. No ammonia is evolved when the C_{12} product is warmed with dilute sodium hydroxide solution but a ketone corresponding to the uptake of a molecule of water can then be isolated as the phenylhydrazone: this addition of water is doubtless again due to the opening of a lactone ring. Hydrolysis with 4N-hydrochloric gives benzoic acid, and the other product is an amino-ketone, since thiocyanate converts it into 2-mercapto-4-methyl-5-glyoxalinylacetic acid (VII; R′ = Me). The constitution of this substance is proved by decarboxylation to 4 : 5-dimethyl-2-mercaptoglyoxaline (VIII; R′ = Me) which on benzylation gives 2-benzylthio-4 : 5-dimethylglyoxaline hydrochloride, also prepared by an independent method (Part VI, *loc. cit.*). (4 : 5-Disubstituted mercaptoglyoxalines frequently melt above 300° so that benzylthio-derivatives serve conveniently for characterisation.)

The compound $C_{12}H_{11}O_3N$ is therefore the azlactone (III; R = Ph, R′ = Me) of β-benzamido-γ-ketovaleric acid. Compounds containing this ring have been prepared by Marrer and Miyamichi (*Helv. Chim. Acta*, 1926, **9**, 336) and by Baker and Ollis (*J.*, 1949, 345) by dehydration of acylamino-acids. The possibility that the substance $C_{12}H_{11}O_3N$, though apparently neutral, was an oxazole (XII; R = Ph, R′ = Me) was considered in view of Wiley's preparation (*J. Org. Chem.*, 1947, **12**, 43) of such compounds by vigorous dehydration of acylamino-ketones prepared from amino-acids. The oxazoles, however, resist hydrolysis by acids, the only recorded hydrolysis being that of 2 : 5-diphenyloxazole from which Gabriel (*Ber.*, 1910, **43**, 136) obtained aminoacetophenone using hydrochloric acid under pressure: 2-phenyloxazole-4-carboxylic acid, for example, can be recovered unchanged after several hours' boiling with concentrated hydrochloric acid.

A third possible structure for the compound $C_{12}H_{11}O_3N$ is (IV; R = Ph, R′ = Me) corresponding to the *N*-acetyl derivative of the β-aminoangelicalactone (Dakin and West, *loc. cit.*). Actually, this structure is realised in a product, m. p. 174°, obtained in variable yield by use of acetic anhydride in boiling acetic acid. This substance shows no ketonic reactions unless first hydrolysed with loss of nitrogen. Like Dakin and West's product it liberates ammonia in warm dilute sodium hydroxide solution. It dissolves in boiling dilute hydrochloric acid with formation of benzamide, carbon dioxide, and diacetyl.

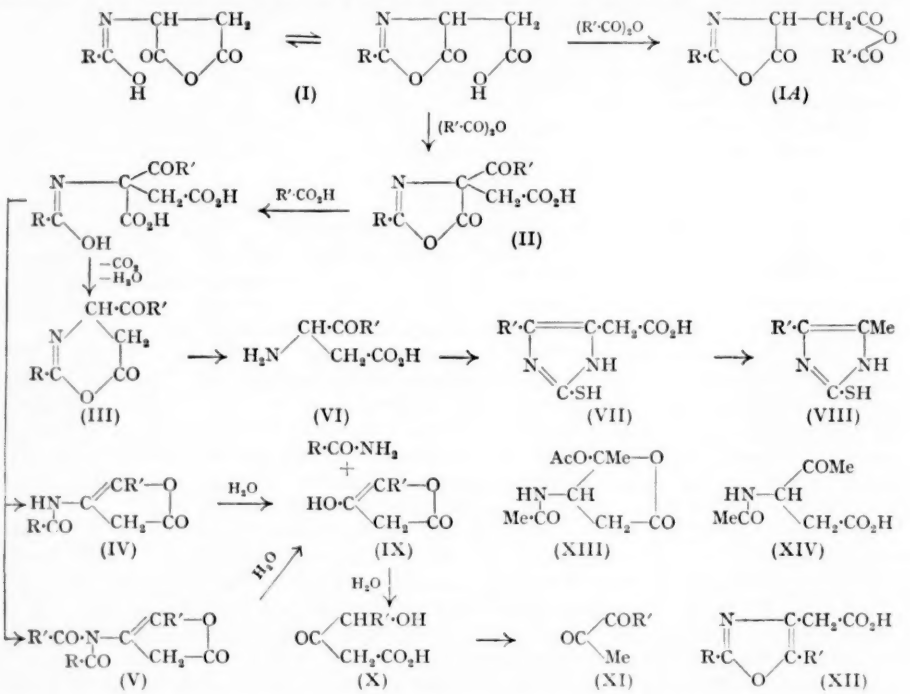
With acetic anhydride and 2-picoline at 100° benzoylaspartic anhydride rapidly gives carbon dioxide and, in almost theoretical yield, a substance $C_{14}H_{13}O_4N$. This material gives reactions similar to those of the C_{12} compound, m. p. 174°, and, in addition, acetic acid is liberated in the hydrolyses with sodium hydroxide and hydrochloric acid. It is possible to obtain after mild acid hydrolysis the phenylhydrazone of a ketone $C_5H_6O_3$ which would correspond to β-keto-γ-valerolactone (IX; R′ = Me).

Dakin and West (*loc. cit.*) suggested that the original product of the action of acetic anhydride on aspartic acid in pyridine was (XIII). On the basis of the analytical results the structure (V; R = Ph, R′ = Me) is assigned to the C_{14} product from benzoylaspartic anhydride. Such a diacylamino-structure is supported by Wiley and Borum's isolation (*J. Amer. Chem. Soc.*, 1950, **72**, 1626) of diacetylglycine ethyl ester from glycine ethyl ester and acetic anhydride in pyridine. It seems probable therefore that in the Dakin and West

reaction the first product is likewise an *N*-diacetyl derivative (V; R = R′ = Me) and that during the working up of the product one acetyl group is lost giving β-acetamidoangelicalactone (IV; R = R′ = Me) and not β-acetamido-γ-ketovaleric acid (XIV). In view of the isolation of the mercaptoglyoxaline, it appears that β-acylamino-γ-ketovaleric acids do not lose their nitrogen on hydrolysis with acid (cf. Dakin and West, *loc. cit.*). The above results, further interpreted, indicate that acids first hydrolyse the C–N linkage of the β-aminoangelicalactone structure and not the lactone ring, otherwise an amino-ketone would result.

In view of the previous work on benzoylaspartic anhydride already referred to there seem reasonable grounds for considering that in the reactions with acetic anhydride in the presence of picoline an oxazolone, generally believed to be an intermediate in the Dakin and West reaction, is the reacting form of the anhydride. In the present case the oxazolone (I) would give the acyloxazolone (II) in accordance with the views of Cleland and Niemann (*J. Amer. Chem. Soc.*, 1949, **71**, 841) and Cornforth and Elliot (*Science*, 1950, **112**, 534). It might on the other hand be argued that the similarity in structure of the benzoylaspartic oxazolone and anhydride might even allow the reaction to proceed with the latter substance.

In the reaction without picoline, however, the behaviour of benzoylaspartic acid is not so readily explained. Such a reaction, as might be expected, is also given by ethyl hydrogen acetamidomalonate, for which a successful Dakin and West reaction has already been reported (Albertson, Tullar, King, Fishburn, and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 1150), but not by benzoylglutamic anhydride or phthalimidosuccinic anhydride for which an oxazolone structure is excluded. It may be that benzoylaspartic anhydride by virtue of its close relation to the oxazolone and its having an additional carboxyl group when compared with



other oxazolones is better able to accommodate the anionic charge which is developed before acylation and therefore requires no basic catalyst. Or perhaps a mixed anhydride of the type (I*A*) is produced: this, after a rearrangement, could also give rise to (II). The fact that there is no reaction between acetylaspartic anhydride and acetic anhydride in the

absence of picoline may be explained by the difference in the mobility of the amide-hydrogen atom, a view which is supported by the differing degree of racemisation of benzoyl-aspartic and acetylaspartic anhydrides in du Vigneaud and Meyer's procedure (Barker, *loc. cit.*).

This common intermediate (II) from the catalysed and the uncatalysed reaction may then, after ring opening, loss of carbon dioxide, and dehydration, give either β-benzamido-γ-ketovaleric acid azlactone (III; R = Ph, R′ = Me) from which the mercaptoglyoxaline (VII; R′ = Me) is obtained, or benzamidoangelicalactone (IV; R = Ph, R′ = Me) as shown in the proposed reaction sequence above.

In the action of the higher homologues of acetic anhydride on benzoylaspartic azlactone, the presence or absence of picoline has no such clear-cut effect as in the case of acetic anhydride: products corresponding to both (III) and (IV) are formed simultaneously. Without picoline, but in boiling xylene which is a convenient solvent, propionic and butyric anhydride give crystalline products (IV; R = Ph, R′ = Et and Pr^n, respectively), from which acylamino-ketones are not obtainable. Since (IV) is more rapidly hydrolysed than (III), mother-liquors yield on hydrolysis for a short time the crystalline γ-keto-acids. In the case of the butyric anhydride derivative, the action of acetic anhydride produces isolatable amounts of the 3-benzamido-4-hydroxyhept-3-enoic lactone (IV; R = Ph, R′ = Pr^n), thus showing the close relation between the two reactions of the acyloxazolone (II). The γ-keto-acids on further hydrolysis with stronger acid lose benzoic acid, and the amino-ketonic acids produced are converted into the corresponding mercaptoglyoxalinyl-acetic acids (VII) by potassium thiocyanate.

With propionic and butyric anhydrides at 100° or the boiling point in presence of picoline benzoylaspartic anhydride gives only oils; however, hydrolysis with hydrochloric acid then enables the benzamido-keto-acids to be isolated in small yield and from these the mercaptoglyoxalines are obtained.

n-Hexanoic anhydride and benzoylaspartic anhydride in xylene give mainly a neutral non-ketonic substance $C_{16}H_{19}O_3N$, corresponding to the unsaturated lactones obtained with the lower homologues. This substance, however, is substantially unaffected by boiling 20% hydrochloric acid. Concentrated hydrochloric acid at 160° converts it into an isomeric acid which, apart from salt formation, is unaffected by sodium hydroxide solution under conditions which liberate benzoic acid from the isomer. This fact, together with the weakly basic nature of the substance, suggests that the benzoyl group is concerned in ring formation. Therefore, the acid is probably 5-*n*-amyl-2-phenyl-4-oxazolylacetic acid (XII; R = Ph, R′ = *n*-amyl). Small quantities of low-melting material encountered in the earlier experiments, particularly in those with butyric anhydride, may have been due to homologous oxazoles formed in a similar way.

Removal of solvent from the mother-liquors of the preceding neutral substance, followed by hydrolysis with concentrated hydrochloric acid, gives a benzamido-keto-acid $C_{16}H_{21}O_4N$ which on further hydrolysis loses benzoic acid to produce the amino-keto-acid from which 4-*n*-amyl-2-mercapto-5-glyoxalinylacetic acid (VII; R′ = *n*-amyl) is obtained as in the cases of the lower homologous anhydrides.

Experimental

Benzoylaspartic Anhydride.—Benzoyl-DL-aspartic acid (5 g.), finely powdered, was warmed on the steam-bath with acetic anhydride (30 ml.) and dissolution was accelerated by shaking. The solution was then filtered and cooled in ice. The anhydride which crystallised as felted needles was washed with light petroleum (yield 4 g.; m. p. 205°). Evaporation of the mother-liquor under reduced pressure gave a further quantity. To remove the last traces of acetic anhydride, which were held rather tenaciously, the product was heated at 70° *in vacuo*.

DL-β-*Benzamido-γ-ketovaleric Azlactone* (III; R = Ph, R′ = Me).—Benzoyl-DL-aspartic anhydride (2 g.) and acetic anhydride (10 ml.) were boiled under reflux till evolution of carbon dioxide ceased (12 minutes). After evaporation *in vacuo*, the sticky residue was crystallised from ethyl acetate containing a little light petroleum (b. p. 40—60°), and then from ethanol or ethyl acetate, giving the *azlactone* as prisms, m. p. 94° (1·5 g.) (Found: C, 66·0; H, 5·2; N, 6·4. $C_{12}H_{13}O_3N$ requires C, 66·4; H, 5·1; N, 6·4%). Treatment with a solution of 2 : 4-dinitrophenylhydrazine in ethanol containing a drop of concentrated sulphuric acid gave yellow needles

of *ethyl* DL-β-*benzamido-γ-ketovalerate* 2 : 4-*dinitrophenylhydrazone*, m. p. 212° (from ethanol–toluene) (Found: C, 53·6; H, 4·7; N, 15·5. $C_{20}H_{21}O_7N_5$ requires C, 54·2; H, 4·7; N, 15·8%). The azlactone dissolved in warm dilute sodium hydroxide solution; the solution was nearly neutralised with hydrochloric acid, and acetic acid and phenylhydrazine hydrochloride were added. After 15 minutes' warming on the steam-bath, β-*benzamido-γ-phenylhydrazonovaleric acid* was removed and recrystallised from ethanol–benzene as pale yellow needles, m. p. 171° (Found: C, 67·1; H, 6·0; N, 12·6. $C_{18}H_{19}O_3N_3$ requires C, 66·6; H, 5·9; N, 12·9%).

2-*Mercapto-5-glyoxalinylacetic Acid.*—β-Benzamido-γ-ketovaleric azlactone (2 g.) was boiled with 4N-hydrochloric acid (15 ml.) under reflux for 1 hour. The benzoic acid was removed from the cooled solution and the filtrate evaporated to dryness *in vacuo*. The evaporation was repeated after the addition of a little water (to remove most of the hydrochloric acid), and the residue, dissolved in water, was warmed on the steam-bath with a few crystals of potassium thiocyanate. After 1 hour the crystals of the 2-*mercapto-5-glyoxalinylacetic acid* were removed from the cooled solution and recrystallised from hot water containing a little ethanol as colourless prisms (0·9 g.), m. p. > 300° (decomp.) (Found: C, 42·0; H, 4·8; N, 16·0. $C_6H_8O_2N_2S$ requires C, 41·8; H, 4·65; N, 16·25%).

2-*Mercapto*-4 : 5-*dimethylglyoxaline.*—The above acid was decarboxylated at 200° under nitrogen (a few minutes). The 2-mercapto-4 : 5-dimethylglyoxaline had m. p. > 300° (from aqueous ethanol). When boiled for 30 minutes with a slight excess of benzyl chloride in ethanol this was converted into 2-*benzylthio*-4 : 5-*dimethylglyoxaline hydrochloride*, m. p. 172° (from alcohol–benzene) (Found: C, 56·6; H, 6·2. $C_{12}H_{15}N_2SCl$ requires C, 56·4; H, 5·9%). This had the same m. p. as, and showed no depression in m. p. when mixed with, a specimen prepared from alanine (Part VI, *loc. cit.*).

3-*Benzamido*-4-*hydroxypent*-3-*enoic Lactone* (β-*Benzamidoangelicalactone*) (IV; R = Ph, R′ = Me).—Benzoylaspartic acid (2 g.) was boiled with acetic acid (10 ml.) and acetic anhydride (10 ml.) for 15 minutes, the solution was evaporated *in vacuo*, and the gummy product dissolved in ethyl acetate. After addition of light petroleum to turbidity, and cooling, crystals of benzoylaspartic anhydride were removed and from the evaporated mother-liquor prisms of β-*benzamidoangelicalactone* gradually separated. Recrystallised from ethyl acetate or ethanol, this had m. p. 174° (Found: C, 66·6; H, 5·0; N, 5·9. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·4%). This substance was neutral in reaction. It dissolved in warm N-sodium hydroxide with the uptake of 1 equivalent of alkali. Warming it with an excess of 3N-sodium hydroxide caused evolution of ammonia and the solution became yellow and eventually blackened, presumably owing to the formation of diacetyl. The substance was dissolved in warm dilute hydrochloric acid and, after addition of water and concentration *in vacuo*, benzamide crystallised. After removal of this the distillate from the neutralised filtrate contained diacetyl as shown by the formation of the bisphenylhydrazone, m. p. 139° and bis-semicarbazone, m. p. 279°.

3-N-*Acetyl*-N-*benzamido*-4-*hydroxypent*-3-*enoic Lactone* (V; R = Ph, R′ = Me).—Benzoylaspartic anhydride (2 g.) was dissolved in acetic anhydride (10 ml.) and 2-picoline (5 ml.) on the steam-bath, carbon dioxide being evolved. After 90 minutes the solution was evaporated to dryness *in vacuo* and the crystalline residue recrystallised in prisms from ethyl acetate. The yield of N-*acetyl*-β-*benzamidoangelicalactone*, m. p. 142°, was 1·8 g. (Found: C, 65·0; H, 5·0; N, 5·45. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%). This substance like that above lost its nitrogen when heated with dilute acid or alkali. The solution in hot dilute hydrochloric acid, when evaporated to dryness *in vacuo*, gave the β-*phenylhydrazono-γ-valerolactone*, m. p. 148°, on appropriate treatment and crystallisation from alcohol–benzene (Found: C, 64·5; H, 5·6; N, 13·2. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

Action of Propionic Anhydride on Benzoylaspartic Anhydride.—Benzoyl-DL-aspartic anhydride (2 g.) was heated at the b. p. with xylene (10 ml.) and propionic anhydride (10 ml.) till evolution of carbon dioxide ceased (20 minutes). After evaporation *in vacuo*, the oily residue, on treatment with a little ethyl acetate, gave colourless crystals of 3-*benzamido*-4-*hydroxyhex*-3-*enoic lactone* (IV; R = Ph, R′ = Et) (0·4 g.). On recrystallisation from ethyl acetate this had m. p. 150° (Found: C, 67·0; H, 5·3; N, 5·9. $C_{13}H_{13}O_3N$ requires C, 67·4; H, 5·6; N, 6·0%). It was hydrolysed by boiling 4N-hydrochloric acid with loss of carbon dioxide and production of benzoic acid, ammonium chloride, and an unidentified ketone. The mother-liquor from the hexenolactone, with dinitrophenylhydrazine in ethanol containing a trace of sulphuric acid, gave yellow needles of *ethyl* DL-3-*benzamido*-4-*ketohexanoate* 2 : 4-*dinitrophenylhydrazone*, m. p. 172° after recrystallisation from ethanol (Found: C, 53·2; H, 5·0; N, 14·0. $C_{21}H_{23}O_7N_5$ requires C, 55·0; H, 5·0; N, 15·3%). Removal of the solvent from the above mother-liquor and hydrolysis of the residue with 4N-hydrochloric acid for a short time yielded

on cooling a semi-solid mixture of benzoic acid and DL-β-*benzamido-γ-ketohexanoic acid* from which the benzoic acid was removed by ether-extraction. The keto-acid recrystallised from ethyl acetate in needles, m. p. 130° (Found: C, 62·7; H, 6·1; N, 5·6. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·6%).

Hydrolysis of the last-named substance with 6N-hydrochloric acid and further treatment as described above for the corresponding acetic anhydride derivative gave *4-ethyl-2-mercapto-5-glyoxalinylacetic acid* (VII; R′ = Et) as tufts of colourless needles, m. p. > 300° (decomp.), from water–ethanol (yield, 50% calc. on the anhydride) (Found: C, 45·9; H, 5·5; N, 14·6. $C_7H_{10}O_2N_2S$ requires C, 45·2; H, 5·4; N, 15·0%). Decarboxylation and benzylation produced *2-benzylthio-4-ethyl-5-methylglyoxaline hydrochloride*, colourless needles (from ethanol), m. p. 153° (Found: C, 57·8; H, 6·2. $C_{13}H_{17}N_2SCl$ requires C, 58·0; H, 6·3%). Identity of this substance with that obtained by the action of benzyl chloride on 4-ethyl-2-mercapto-5-methylglyoxaline, prepared by another method, proved its constitution.

When benzoylaspartic anhydride (2 g.) was heated on the steam-bath or at the b. p. for 1½ hours with propionic anhydride (10 ml.) and 2-picoline (5 ml.) no crystallisation took place after evaporation of the solution *in vacuo*. The oily residue on hydrolysis with boiling 6N-hydrochloric acid and further treatment as described above gave 0·3 g. of 4-ethyl-2-mercapto-5-glyoxalinylacetic acid.

Action of n-*Butyric Anhydride on Benzoylaspartic Anhydride.*—Benzoyl-DL-aspartic anhydride (2 g.) was boiled with xylene (10 ml.) and *n*-butyric anhydride (10 ml.) till carbon dioxide evolution ceased (35 minutes). After evaporation *in vacuo*, there was obtained 0·3 g. of crystals which recrystallised from ethyl acetate in colourless needles, m. p. 122° (Found: C, 69·1; H, 5·9; N, 5·6. $C_{14}H_{15}O_3N$ requires C, 68·7; H, 6·1; N, 5·7%). They gave no reaction with dinitrophenylhydrazine and liberated carbon dioxide and benzoic acid with hot dilute hydrochloric acid and were therefore *3-benzamido-4-hydroxyhept-3-enoic lactone* (IV; R = Ph, R′ = Pr^n). A small sample of the non-crystalline material from this reaction on treatment with dinitrophenylhydrazine in ethanol containing a trace of sulphuric acid gave *ethyl* DL-*3-benzamido-4-ketoheptanoate* **2** : *4-dinitrophenylhydrazone* as yellow needles (from ethanol), m. p. 163° (Found: C, 55·3; H, 5·4; N, 14·7. $C_{22}H_{25}O_7N_5$ requires C, 55·7; H, 5·3; N, 14·8%. The bulk of the non-crystalline material was heated with boiling 4N-hydrochloric acid for 30 minutes and cooled. The insoluble oily layer solidified and was removed. Extraction of the benzoic acid left a crystalline residue (0·8 g.) of DL-β-*benzamido-γ-keto*-n-*heptanoic acid*, needles (from ethyl acetate), m. p. 146° (Found: C, 63·6; H, 6·3; N, 5·1. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). The last-named substance on hydrolysis with 6N-hydrochloric acid for 3 hours and further treatment as described above for the lower homologue gave *2-mercapto*-4-n-*propyl-5-glyoxalinylacetic acid* (VII; R′ = Pr^n), m. p. 264° (after sintering at 240°), prisms from aqueous ethanol (0·4 g. from 0·5 g. of the keto-acid) (Found: C, 48·0; H, 5·9; N, 14·0. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0; N, 14·0%). When the reaction between *n*-butyric anhydride and benzoylaspartic anhydride was carried out in 2-picoline as previously described an oil was obtained, which afforded β-benzamido-γ-keto-*n*-heptanoic acid and 2-mercapto-4-*n*-propyl-5-glyoxalinylacetic acid. Decarboxylation of the last substance at 240° in nitrogen gave *2-mercapto-5-methyl*-4-n-*propylglyoxaline*, prisms (from aqueous ethanol), m. p. 267° (Found: C, 53·7; H, 7·6. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%).

Action of n-*Hexanoic Anhydride on Benzoylaspartic Anhydride.*—Benzoyl-DL-aspartic anhydride (2 g.) was boiled with xylene (15 ml.) and *n*-hexanoic anhydride (15 ml.) till carbon dioxide evolution ceased (45 minutes). After evaporation under reduced pressure, the solution crystallised and *3-benzamido-4-hydroxynon-3-enoic lactone* (1·5 g.) (IV; R = Ph, R′ = *n*-amyl) was collected. This substance, recrystallised from ethyl acetate in colourless needles, had m. p. 135° (Found: C, 69·7; H, 7·1; N, 5·4. $C_{16}H_{19}O_3N$ requires C, 70·4; H, 7·0; N, 5·1%). It was neutral and was hardly affected by boiling concentrated hydrochloric acid for 6 hours. Concentrated hydrochloric acid at 160° (4 hours) converted it almost quantitatively into an isomeric *acid* which, being soluble in the hydrochloric acid, was obtained after evaporation *in vacuo*. This acid was recrystallised from ethyl acetate–light petroleum or aqueous ethanol as felted needles, m. p. 96° (Found: C, 69·8; H, 7·0; N, 4·9. $C_{16}H_{19}O_3N$ requires C, 70·4; H, 7·0; N, 5·1%). It gave no ketonic reactions, was unaffected by boiling 2N-sodium hydroxide, and was recovered unchanged by distillation at 1 mm. after having been heated to 240° in nitrogen.

The excess of hexanoic anhydride in the mother-liquor from the nonenolactone above was removed by distillation at 1 mm. The oily residue on treatment with dinitrophenylhydrazine in ethanol gave yellow needles of *ethyl* DL-β-*benzamido-γ-keto*-n-*nonanoate* **2** : *4-dinitrophenylhydrazone*, m. p. 155° (from ethanol) (Found: C, 57·0; H, 5·6. $C_{24}H_{29}O_7N_5$ requires C, 57·7;

H, 5·8%). After hydrolysis of the oily residue with boiling 20% hydrochloric acid and cooling, the crystalline material obtained was collected and after treatment with sodium carbonate and reprecipitation with acid recrystallised from ethyl acetate–light petroleum, giving colourless needles of DL-*β-benzamido-γ-keto*-n-*nonanoic acid*, m. p. 127° (0·7 g. from 2 g. of benzoylaspartic anhydride) (Found: C, 66·4; H, 7·3. $C_{16}H_{21}O_4N$ requires C, 66·1; H, 7·2%). The benzoyl group was removed by hydrolysis with concentrated hydrochloric acid at 160° for 4 hours, and treatment with potassium thiocyanate as described above gave colourless plates of 4-n-*amyl*-2-*mercapto*-5-*glyoxalinylacetic acid*, m. p. 174° (decomp.) (from aqueous ethanol) (60%) (Found: C, 52·8; H, 7·0; N, 12·3. $C_{10}H_{16}O_2N_2S$ requires C, 52·7; H, 7·0; N, 12·3%). Decarboxylation of the acid at 175° gave smoothly 4-n-*amyl*-2-*mercapto*-5-*methylglyoxaline*, prisms (from aqueous ethanol), m. p. 228° (Found: C, 58·9; H, 8·7. $C_9H_{16}N_2S$ requires C, 58·7; H, 8·7%).

Phthalimidosuccinic Anhydride.—King and Kidd's method (*J.*, 1949, 3315) for glutamic acid was followed. DL-Aspartic acid (3·0 g.), phthalic anhydride (3·1 g.), and pyridine (12 ml.) were boiled under reflux for 2 hours, filtered, and concentrated *in vacuo* to a thick syrup. Boiling this with acetic anhydride for 3 minutes and then cooling gave DL-*phthalimidosuccinic anhydride* (3·8 g., 69%), m. p. 227° (from acetic anhydride) (Found: C, 58·9; H, 3·0. $C_{12}H_7O_5N$ requires C, 58·8; H, 2·9%).

Reaction between Acetic Anhydride and Ethyl Hydrogen Acetamidomalonate.—Ethyl hydrogen acetamidomalonate (1 g.) was dissolved rapidly in acetic anhydride (10 ml.) at 100° and the solution concentrated *in vacuo*. On cooling, *ethyl hydrogen* NN-*diacetylaminomalonate* (0·4 g.) crystallised in plates, m. p. 119° (decomp.) (Found: C, 46·5; H, 5·6. $C_9H_{13}O_6N$ requires C, 46·8; H, 5·6%). When the above reactants were refluxed, carbon dioxide was evolved and the oily residue obtained after evaporation *in vacuo* was boiled for 30 minutes with 3N-hydrochloric acid containing potassium thiocyanate. Crystals of ethyl 2-mercapto-4-methylglyoxaline-5-carboxylate which came down on concentration of the solution were recrystallised from aqueous ethanol and then had m. p. 237° (decomp.).

I thank Mr. R. A. F. Bullerwell for preparing the phthalimidosuccinic anhydride and Mr. J. O. Stevens for technical assistance.

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213. *The Electrolytic Conductance of Solutions of Phosphorus Pentachloride.*

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The electrolytic conductances at 25° of phosphorus pentachloride dissolved in phosphorus oxychloride, benzoyl chloride, nitrobenzene, benzonitrile, and acetonitrile have been measured. The solutions in the last solvent have larger specific conductances than similar solutions in the other solvents. Transport-number experiments support the existence of the ions PCl_4^+ and PCl_6^- in solution. Attempts to prepare salts containing the latter ion have been unsuccessful.

THE conductance of a solution of phosphorus pentachloride in nitrobenzene was reported by Holroyd, Chadwick, and Mitchell (*J.*, 1925, **127**, 2492). No measurements of its conductance in other solvents except bromine (Plotnikov and Jakubson, *Z. phys. Chem.*, 1928, **138**, 235) and phosphorus oxychloride (Gutmann, *Monatsh.*, 1952, **83**, 39) had been made. The ionic nature of solid phosphorus pentachloride was established by *X*-ray investigation (Clark, Powell, and Wells, *J.*, 1942, 642); however, in the liquid phase the very low conductance (Voigt and Biltz, *Z. anorg. Chem.*, 1924, **133**, 277) together with other data suggested that the condition was primarily a molecular one. No consideration has been given to the state of phosphorus pentachloride in solution, where under certain conditions the simple molecular form might predominate, whilst under others considerable ionisation might occur. Measurements of the specific and equivalent conductivities in various solvents under strictly anhydrous conditions are given in the Table. In each case

the solvent and phosphorus pentachloride were purified thoroughly before the solutions were prepared. Measurements were made as soon as possible (within a few hours) after the start of the experiment, since in many cases the readings were inclined to drift when

Electrolytic conductance of phosphorus pentachloride at 25°.

Solvent	PCl_5, mole/l.	κ, mho/cm.	Equivalent conductivity based on PCl_5	Equivalent conductivity based on $(PCl_5)_2$
$POCl_3$ *	0·409	$1·99 \times 10^{-4}$	0·49	0·98
Ph·COCl	0·0325	$5·09 \times 10^{-5}$	1·57	3·14
Dioxan	0·0825	$<10^{-7}$	0	0
Et_2O	*ca.* 0·05	$<10^{-7}$	0	0
$Ph·NO_2$	0·0517	$1·77 \times 10^{-4}$	3·43	6·86
	0·0470	$1·57 \times 10^{-4}$	3·39	6·78
	0·0174	$5·75 \times 10^{-5}$	3·29	6·58
	0·0137	$4·51 \times 10^{-5}$	3·30	6·60
	0·00480	$1·63 \times 10^{-5}$	3·40	6·80
	0·00137	$5·00 \times 10^{-6}$	3·64	7·28
Ph·CN	0·0301	$3·08 \times 10^{-5}$	1·03	2·06
Me·CN	0·1870	$4·92 \times 10^{-3}$	26·3	52·6
	0·0722	$2·16 \times 10^{-3}$	29·2	58·4
	0·0495	$1·41 \times 10^{-3}$	30·0	60·0
	0·00554	$1·91 \times 10^{-4}$	34·5	69·0

* Gutmann (*loc. cit.*) gives $\Lambda = 0·49$ at 20° and a concentration of 0·596 mole of PCl_5/l.

the solutions were kept, probably owing to reaction between the halide and the solvent. The effects of the addition of small amounts of water (0·1 ml. per 10—15 g. of solvent) and of change of temperature were noted for each solution. The former led to a marked change in the results, usually an increase in the conductance, presumably owing to the presence of the products of hydrolysis. Increase in temperature resulted in an increase in the conductance in benzonitrile and a decrease in benzoyl chloride, nitrobenzene, acetonitrile, and phosphorus oxychloride. It seemed of importance to establish the complete absence of reaction between the phosphorus pentachloride and the solvent within the time required for the experiment, and this was achieved in the case of acetonitrile by the quantitative recovery of pure phosphorus pentachloride from the solution, after the solution had been kept for a few hours, during which time the conductance remained unchanged. Longer storage (24 hours) resulted in slight reaction, as shown by the appearance of hydrogen chloride in the solution, the presence of readily volatile phosphorus compounds, and a marked change in the conductance. The application of this method (*i.e.*, recovery of the solute) was impossible in the case of the higher-boiling solvents such as nitrobenzene, but in these cases the reproduceability and constancy of the conductance results, coupled with the absence of hydrogen chloride, suggested that no reaction had occurred. Hydrogen chloride, an expected product of any reaction which might occur, was shown to be absent in all cases by pumping out the solutions and examining any volatile materials obtained. De Konnick and Marquart (*Ber.*, 1872, **5**, 11) had shown that phosphorus pentachloride and nitrobenzene do not react to any appreciable extent.

The results show that in the solvents investigated phosphorus pentachloride varies considerably in the extent of its dissociation into ions. The determining factor would appear to be the ability of the solvent to stabilise the ionisation by complex formation, rather than the effect of its dielectric constant. The data for the equivalent conductance shown in the Table (col. 4) are expressed on the basis of moles of phosphorus pentachloride (PCl_5) per l. of solution. An alternative and more precise presentation is in terms of the ionisation

$$2PCl_5 \rightleftharpoons PCl_4^+ + PCl_6^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(A)}$$

and is expressed as moles of $(PCl_5)_2$ per litre. Data for acetonitrile solutions on this basis are shown in col. 5. It was not possible to obtain results at a sufficiently low concentration to make feasible the extrapolation of the equivalent conductivity to infinite dilution, so no reliable comparison with other uni-univalent electrolytes (Λ_∞ 150—200) is possible. Failure to obtain conductance data at low concentrations was in the main due to the difficulties arising from traces of water and impurities.

Electrolysis of a solution of phosphorus pentachloride in acetonitrile, by means of

smooth platinum electrodes and a cell designed to prevent mixing by diffusion, leads to concentration changes in the anolyte and catholyte which are completely in accord with ionisation (A). Thus, if it is assumed that no phosphorus or chlorine is lost from the solution during electrolysis, then $\Delta_{Cl} = x(10n^+ - 6)$ and $\Delta_P = x(1 - 2n^+)$, where Δ_{Cl} and Δ_P are the changes in g.-atoms of chlorine and phosphorus in the catholyte and anolyte respectively, x is the number of Faradays passed during the electrolysis, and n^+ is the transport number of the cation at the concentration studied. The corresponding changes for the ionisation $PCl_5 \rightleftharpoons PCl_4^+ + Cl^-$ are $\Delta_{Cl} = x(5n^+ - 1)$ and $\Delta_P = -xn^+$.

The electrode processes occurring during the electrolysis are envisaged as

Anode : $PCl_6^- - e \longrightarrow [PCl_6] \longrightarrow PCl_5 + [Cl]$

$[Cl] + CH_3{\cdot}CN \longrightarrow$ Chlorinated compounds

Cathode : $PCl_4^+ + e \longrightarrow [PCl_4] \longrightarrow PCl_3 + PCl_5$.

The presence of phosphorous acid in the hydrolysed catholyte and of free chlorine in the anolyte confirms the suggested electrode reactions. A transport experiment in nitrobenzene has given results which are also in agreement with the ionisation (A).

In view of the absence of information, other than the conductances reported above, on the state of phosphorus pentachloride in solution, an attempt was made to measure the molecular weight in a variety of solvents. Only nitrobenzene possessed suitable properties for a sufficiently precise molecular-weight determination. Acetonitrile is unsuitable, having too low a melting point for cryoscopic measurements and being too reactive at the boiling point for ebullioscopic measurements. Results for the molecular weight by depression of freezing point in nitrobenzene, carried out under strictly anhydrous conditions, show that the association to double molecules occurs to a negligible extent in this solvent.

The occurrence of the PCl_6^- ion in acetonitrile solution suggested that this solvent might be a suitable one for the preparation of other salts containing this anion and other alkali-metal cations. These attempted preparations and others involving direct interaction of phosphorus pentachloride and an alkali-metal halide were unsuccessful. Similar experiments by Gutmann (*Monatsh.*, 1952, **83**, 583) were also unsuccessful. It thus appears that compounds based on a lattice comprising PCl_6^- and a simple cation are unstable under the conditions examined. Compounds which are essentially ionic, based on the PCl_4^+ ion, have been prepared and will be reported in a later communication.

In view of the existence of numerous addition compounds of halides with nitriles and nitro-compounds, and the possibilitity of obtaining evidence for the stabilisation of the ionised form of phosphorus pentachloride, the formation of solvates of phosphorus pentachloride was of interest. No evidence for solvates of phosphorus pentachloride with acetonitrile or nitrobenzene was obtained, a surprising fact in view of the existence of $SbCl_5,CH_3{\cdot}CN$ (Henke, *Annalen*, 1858, **106**, 281) and $2SbCl_5,3C_6H_5{\cdot}NO_2$ (Rosenheim and Stellman, *Ber.*, 1901, **34**, 3382).

The conductance of phosphorus pentabromide in bromine (Plotnikov, *Z. phys. Chem.*, 1904, **48**, 220) in liquid sulphur dioxide and arsenic trichloride (Walden, *ibid.*, 1903, **43**, 434) and in nitrobenzene (Finkelstein, *ibid.*, 1925, **115**, 303) has been measured. An exploratory experiment using acetonitrile, but without intense purification of the phosphorus pentabromide, gave a value of $\kappa = 0{\cdot}53 \times 10^{-4}$ mho/cm. at a concentration of 0·0078 mole of (PBr_5) per l. of solvent at 20°, corresponding to an equivalent conductance of 6·9. Acetonitrile reacts more readily with phosphorus pentabromide than with the pentachloride. Preliminary experiments show that phosphorus pentafluoride in acetonitrile gives a conducting solution.

Experimental

Materials.—Phosphorus pentachloride was prepared by reaction of pure phosphorus trichloride (b. p. 75—76°) with an excess of pure dry chlorine. The resulting solid was stored in a glass-stoppered bottle in a desiccator until required, and was sublimed in a vacuum on to a cold finger before use. Solvents were ordinary commercial chemicals purified by storage over suitable drying agents followed by fractionation or distillation until a material of sufficient purity was obtained. Nitrobenzene and acetonitrile were purified according to the methods

of Kraus and Taylor (*J. Amer. Chem. Soc.*, 1947, **69**, 1731) and of Smith and Witten (*Trans. Faraday Soc.*, 1951, **47**, 1304), respectively. All the solvents except phosphorus oxychloride and nitrobenzene were finally distilled from phosphoric oxide before use. Pure solvents had the following specific conductances (κ) in mho/cm.: phosphorus oxychloride 10^{-6}, benzoyl chloride 10^{-5}, dioxan $<10^{-7}$, diethyl ether $<10^{-7}$, nitrobenzene 10^{-7}, benzonitrile $2{\cdot}5 \times 10^{-6}$, acetonitrile 4×10^{-6}.

Measurement of Conductance.—The various solutions were prepared by distilling the solvent in a vacuum on to the solid phosphorus pentachloride, which had previously been kept at room temperature under vacuum to remove any traces of volatile impurities. Dissolution was speeded in most cases by gentle agitation by means of a current of thoroughly dry air, and the solution was then transferred by a difference in pressure to a cell of the pipette type with smooth platinum electrodes each 1 sq. cm. in area (cell constant 0·463). Measurements of conductance were made by using a Mullard conductance bridge, type B 7566, and are considered to be accurate to $\pm 2\%$. The cell and adjoining tubes were kept at a constant temperature in a water thermostat.

Concentrations were determined by weighing a sample of solution and adding it to an excess of water or dilute alkali. The procedure which followed varied from solvent to solvent but was essentially the removal of any unwanted solvent, followed by an adjustment of the solution to the correct conditions for precipitation. The phosphorus pentachloride was then usually determined by precipitation of the chloride as silver chloride. Where this was impossible the pentachloride was determined as phosphorus and weighed as $P_2O_5.24MoO_3$.

Transport Experiments.—Solutions of phosphorus pentachloride were prepared as in the experiments described above. The solution was transferred by a slight pressure difference to a cell in the form of an H. The two compartments were separated by a sintered plate, the arms of the cell having at their ends the electrodes, which were of smooth platinum, 1 sq. cm. in area. Taps were provided to empty the two compartments into sampling vessels. The cell was connected in series with a milliammeter and silver coulometer, and connected to a 20-v battery supply. The amounts of phosphorus and chlorine in the anolyte and catholyte were determined by standard procedures after the solutions had been fully hydrolysed and oxidised. The results of a series of experiments lead to values for the transport number of the cation, $n^+ = 0{\cdot}37$, 0·40, 0·41, and 0·41 measured at 20° in acetonitrile (M $\sim$ 0·05—0·1) and $n^+ = 0{\cdot}65$ in nitrobenzene under similar conditions. In both cases ionisation (A) fits the results completely.

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UNIVERSITY OF GLASGOW. [*Received, December 3rd*, 1952.]

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214. *The Chemistry of Extractives from Hardwoods. Part XI.* The Isolation of a Diterpene Ester (Methyl Vinhaticoate), and of* 6 : 7 : 3′ : 4′-*Tetrahydroxyflavanone (Plathymenin), and* 2 : 4 : 5 : 3′ : 4′-*Pentahydroxychalkone* (neo*Plathymenin*), *from* Plathymenia reticulata.

By F. E. KING, T. J. KING, and K. G. NEILL.

The light petroleum-soluble constituents of the heartwood of *Plathymenia reticulata* include a crystalline methyl ester of a diterpene, vinhaticoic acid, $C_{20}H_{28}O_3$, in which the presence of a furan ring has been demonstrated. Further extraction with ether yields 6 : 7 : 3′ : 4′-tetrahydroxyflavanone (plathymenin), and also the corresponding chalkone (*neo*plathymenin), the principal crystalline pigment of this deep yellow wood.

THE timber vinhatico is a brilliant yellow or brownish-yellow lustrous wood derived either from *Chloroleucon vinhatico* Record or from *Plathymenia reticulata* Benth., both of which are Brazilian trees of the family *Leguminosae*. A quantity of this timber, obtained commercially and identified in the D.S.I.R. Forest Products Research Laboratory as *P. reticulata*, has been extracted and new crystalline products have been isolated.

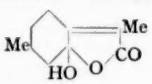
* Part X, *J.*, 1952, 4752.

When dissolved in methanol, the oil isolated by light petroleum yielded a compound $C_{21}H_{30}O_3$, which comprises 1½% of the weight of the wood and is the methyl ester of a diterpene acid. Hydrolysis of the carbomethoxy-group necessitated the vigorous treatment with alkali usually associated with sterically hindered, *e.g.*, tertiary, carboxylic esters. The resulting acid, $C_{20}H_{28}O_3$, vinhaticoic acid, sustained no further change during the hydrolysis, the original ester being recovered by treatment with diazomethane. Methyl vinhaticoate was also obtained by the action of methyl sulphate on the sodium salt, from which the ethyl ester was similarly prepared.

When reduced catalytically, methyl vinhaticoate absorbed two mols. of hydrogen, and the presence of two olefinic bonds was confirmed by titration with monoperphthalic acid. The preparation from the ester and maleic anhydride of an addition compound proved the diene system to be conjugated and, in view of the unreactive nature of the third oxygen atom, it suggested that the conjugated system might form part of a furan ring. In agreement with this hypothesis the maleic anhydride adduct proved to be relatively unstable, and the ultra-violet spectrum of methyl vinhaticoate exhibited an absorption maximum at 220 mμ. A ketone, $C_{23}H_{32}O_4$, obtained from methyl vinhaticoate by the action of acetic anhydride and stannic chloride, reagents which do not readily attack hydrocarbon nuclei, is doubtless formed as a result of acylation in the furan ring.

Evidence confirming the existence of a furan residue in vinhaticoic acid is to be found in the close resemblance between certain reactions of its methyl ester and those of the authentic furano-hydrocarbon menthofuran, $C_{10}H_{14}O$ (I). The latter is readily oxidised

(I)

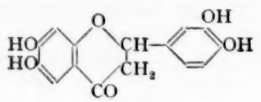


(II)

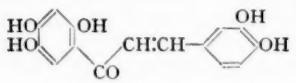
(III)

by various reagents, including hydrogen peroxide, thereby forming a weakly acidic compound $C_{10}H_{14}O_3$, to which Woodward and Eastman (*J. Amer. Chem. Soc.*, 1950, **72**, 399) have recently attributed the structure (II). Analogously, the perphthalic acid oxidation product of methyl vinhaticoate contains two additional oxygen atoms and is weakly acidic. Moreover, the latter yields when fused an anhydro-compound, $C_{21}H_{28}O_4$, thus further resembling (II), which, as Woodward and Eastman have shown, is dehydrated with potassium hydrogen sulphate to the compound (III). From other experiments shortly to be described it has been established that the furan ring of vinhaticoic acid, which is unsubstituted at positions 2 and 3, is fused to a perhydrophenanthrene nucleus.

After extraction by light petroleum the powdered wood was exhausted with boiling ether and the product separated with ethyl acetate into a cream-coloured solid $C_{15}H_{12}O_6$ (A) comprising 5·3% of the weight of wood, and a more soluble isomer (B) amounting when crystallised to 2%. (A), termed plathymenin, formed a tetra-acetate and tetramethyl ether, and its colour reactions were indicative of a flavanone. Oxidation of the tetramethyl ether gave 2-hydroxy-4 : 5-dimethoxybenzoic acid and veratric acid, which were converted into their respective methyl esters and thus separated by alkali, so proving the constitution of plathymenin to be 6 : 7 : 3′ : 4′-tetrahydroxyflavanone (IV). The tetramethyl ether, already synthesised by Bargellini and Marini-Bettolo (*Gazzetta*, 1940, **70**, 170), was oxidised by selenium dioxide to the corresponding tetramethoxyflavone.



(IV) Plathymenin



(V) *neo*Plathymenin

The bright orange *neo*plathymenin (B), $C_{15}H_{12}O_6$, which contributes very considerably to the colour of the wood, displayed properties typical of a polyhydroxychalkone. Moreover, it formed a pentamethyl ether identical with that obtained from plathymenin by methylation in alkaline solution, thus revealing its structure as 2 : 4 : 5 : 3′ : 4′-pentahydroxychalkone (V). This was confirmed when *neo*plathymenin was obtained from

plathymenin by mild alkaline hydrolysis; the action of alkali on *O*-tetramethylplathymenin gave 2-hydroxy-4 : 5 : 3′ : 4′-tetramethoxychalkone, oxidised by hydrogen peroxide to 3-hydroxy-6 : 7 : 3′ : 4′-tetramethoxyflavone (Bargellini and Marini-Bettolo, *loc. cit.*). *neo*Plathymenin thus resembles the isomeric 2 : 3 : 4 : 3′ : 4′-pentahydroxychalkones, okanin and *iso*okanin (King and King, *J.*, 1951, 569), in being a member of the comparatively rare group of naturally occurring chalkones. Both plathymenin and *neo*plathymenin contain the hydroxyquinol nucleus which though found in certain natural coumarins, *e.g.*, æsculetin (6 : 7-dihydroxycoumarin), has not hitherto been encountered among natural products of the flavone or *iso*flavone groups.

Seikel and Geissman (*J. Amer. Chem. Soc.*, 1950, **72**, 5720) have obtained a pigment (stillopsin) from *Coreopsis stillmanii* which is a hexoside of 2 : 4 : 5 : 3′ : 4′-pentahydroxychalkone. The free chalkone was not isolated but was identified by ring-closure and methylation to 6 : 7 : 3′ : 4′-tetramethoxyflavanone which was synthesised.

Experimental

Methyl Vinhaticoate.—The dark-brown oil obtained by continuous extraction of powdered vinhatico (2½ kg.) with boiling light petroleum (b. p. 60—80°) for 16 hours was dissolved in an equal volume of methanol, and the solution set aside at 0°. The deposit of *methyl vinhaticoate*, crystallised once again from methanol (charcoal), formed nearly colourless prisms (38—40 g.), m. p. 106°, raised by further crystallisation to 108°, $[\alpha]_D^{18}$ +66·9° (in $CHCl_3$) (Found: C, 76·1, 76·4; H, 9·3, 9·0; OMe, 9·9. $C_{20}H_{27}O_2$·OMe requires C, 76·3; H, 9·15; OMe, 9·4%). Light absorption in *n*-hexane: max. at 220 mμ (log ε = 3·88). The ester is easily soluble in most organic solvents but only sparingly in methanol and ethanol. When reduced in acetic acid containing platinum oxide the ester (32·1 mg.) absorbed 4·11 c.c. of hydrogen (theory for $2H_2$, 4·36 c.c.).

Methyl vinhaticoate (1 g.) and maleic anhydride (0·5 g.) in benzene (10 c.c.) at room temperature gave in 4 days an *adduct* (yield after concentration, 83%) crystallising from acetone in large hexagonal tablets, m. p. 140° (Found: C, 69·7; H, 7·4. $C_{25}H_{32}O_6$ requires C, 70·1; H, 7·5%). Methyl vinhaticoate was recovered when the adduct (0·2 g.) was boiled for 10 minutes with 2N-sodium hydroxide (10 c.c.).

Vinhaticoic Acid.—A solution of potassium hydroxide (10 g.) in ethanol was concentrated in a copper flask, and when the temperature reached 160°, methyl vinhaticoate (4 g.) was added and the mixture kept at 160—170° for 2 hours. After extraction with hot water (150 c.c.) and acidification, the gummy product was purified by crystallising the sodium salt (long silky needles, m. p. >350°) from 3% aqueous sodium hydroxide. The salt with hydrochloric acid gave *vinhaticoic acid* (3·25 g.) which from 75% ethanol formed shining plates, m. p. 153—154°, $[\alpha]_D^{18}$ +73° (in $CHCl_3$) (Found: C, 76·3; H, 9·0%; equiv., 315. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%; equiv., 316). The acid dissolves easily in organic solvents except light petroleum.

The sodium salt (0·5 g.) in acetone with methyl sulphate gave overnight at room temperature methyl vinhaticoate (0·38 g. from methanol), m. p. 107°, also formed from the acid with ethereal diazomethane during 1 hour.

Ethyl sulphate and the sodium salt in acetone gave *ethyl vinhaticoate*, shining rods, m. p. 80—81° (from aqueous ethanol), $[\alpha]_D$ +58·7° (in $CHCl_3$) (Found: C, 76·5; H, 9·1. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

Oxidation of Methyl Vinhaticoate with Monoperphthalic Acid.—(*a*) Methyl vinhaticoate (1·0091 g.) consumed in 250 hours at 0° monoperphthalic acid equivalent to 161 c.c. of 0·0813N-thiosulphate, *viz.*, 2·14 mols.

(*b*) After 100 hours at room temperature, a solution of the methyl ester (6·5 g.) in chloroform (100 c.c.) and of N-ethereal perphthalic acid (150 c.c.) was filtered from precipitated phthalic acid and washed with aqueous potassium iodide and sodium thiosulphate. Evaporation left a *product* crystallising from methanol in large glistening rhombic tablets (4·75 g.), m. p. 210—212° which became opaque, gradually at room temperature, rapidly at 100° (Found: C, 65·9; H, 8·3. $C_{21}H_{30}O_5,H_2O$ requires C, 66·3; H, 8·5. Found, in dried specimens: C, 69·5; H, 8·2; OMe, 8·7. $C_{20}H_{27}O_4$·OMe requires C, 69·6; H, 8·3; OMe, 8·6%).

The oxidation product dissolved in warm aqueous sodium carbonate or hydroxide, the sodium salt separating in large plates, and it was recovered unchanged on acidification. When cautiously heated above 210° for 5 minutes the *anhydro*-derivative was obtained in needles, m. p. 142—143°, from 80% methanol (Found: C, 73·4; H, 8·1. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%), insoluble in aqueous alkalis and more readily soluble in organic solvents than its precursor.

Methyl Acetylvinhaticoate.—Gradual addition of stannic chloride (1 c.c.) to a mixture of methyl vinhaticoate (2 g.) and acetic anhydride (0·65 c.c.) in benzene (25 c.c.) led to an exothermic reaction. After 4 hours the purple solution was poured on ice, and the ether-soluble product isolated and dissolved in ethanol (5 c.c.). The resulting crude *ketone* (1·2 g.) when repeatedly crystallised from ethanol and light petroleum (charcoal) formed nearly colourless needles, m. p. 162° (Found: C, 73·7; H, 8·95. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%). The *semicarbazone*, rhombic tablets from ethanol, had m. p. 246—248° (Found: C, 67·5; H, 7·9; N, 9·2. $C_{24}H_{35}O_4N_3$ requires C, 67·1; H, 8·2; N, 9·8%).

Plathymenin and neo*Plathymenin.*—The powdered wood (1·7 kg.) already treated with light petroleum was continuously extracted with boiling ether (4—5 l.) for 2—3 days. The separated yellow solid (A) was collected and the solution evaporated; digestion of the residue with boiling ethyl acetate left a solid (B) which was combined with (A) and crystallised from water containing a little sulphur dioxide. 6 : 7 : 3′ : 4′-*Tetrahydroxyflavanone* (*plathymenin*) (90 g., 5·3%) crystallised in pale cream-coloured needles, m. p. 229° (decomp.) (Found: C, 62·2; H, 4·2. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%), soluble to a colourless solution in sodium hydrogen carbonate and deep red in sodium carbonate. Its solutions in concentrated hydrochloric and in sulphuric acid are bright red and its ferric reaction is green. With magnesium and hydrochloric acid the flavanone gives first a faint pink and finally an intense blue colour.

Evaporation of the ethyl acetate solution from which product (B) had been separated and extraction of the residue with boiling water gave a solution from which crystallised 2 : 4 : 5 : 3′ : 4′-*pentahydroxychalkone* (neo*plathymenin*) (34 g., 2%), orange plates, m. p. 232° (decomp)., from aqueous methanol (Found: C, 62·7; H, 4·5%). It dissolves in aqueous sodium hydrogen carbonate to an orange solution which with sodium hydroxide becomes deep red. The sulphuric acid solution is orange and the ferric reaction of the chalkone is dark brown. No colour is formed on reduction with magnesium and hydrochloric acid. Further small amounts of plathymenin (6 g.) and of *neo*plathymenin (3 g.) were isolated from the ethyl acetate-soluble portion of the material extracted by acetone from the wood following its treatment with ether.

O-*Tetra-acetylplathymenin*, prepared with acetic anhydride and sodium acetate, crystallised from methanol in stout rectangular prisms, m. p. 149—151° (Found: C, 60·4; H, 4·6; OAc, 39·4. $C_{23}H_{20}O_{10}$ requires C, 60·5; H, 4·4; 4OAc, 37·7%). Plathymenin (2 g.) with ethereal diazomethane gave the tetramethyl ether (1·4 g.), needles, m. p. 161°, from methanol [Found: C, 66·4; H, 5·9; OMe, 35·9. Calc. for $C_{15}H_{18}O_2(OMe)_4$: C, 66·3; H, 5·85; OMe, 36·1%]. Bargellini and Marini-Bettolo (*loc. cit.*) give for 6 : 7 : 3′ : 4′-tetramethoxyflavanone, m. p. 161°.

O-*Penta-acetyl*neo*plathymenin*, from the chalkone, acetic anhydride, and perchloric acid, crystallised from ethyl acetate–light petroleum in long cream-coloured needles, m. p. 155—156° (Found: C, 60·3; H, 4·8. $C_{25}H_{22}O_{11}$ requires C, 60·2; H, 4·45%). *O*-Pentamethyl*neo*plathymenin, prepared by shaking a solution of either plathymenin or *neo*plathymenin (1 g.) in 30% aqueous sodium hydroxide (40 c.c.) containing sodium dithionite (0·05 g.) with methyl sulphate (12 c.c.), crystallised from aqueous methanol in yellow plates (0·6 g.), m. p. 158—159° (Found: C, 66·8; H, 6·0; OMe, 42·8. Calc. for $C_{20}H_{22}O_6$: C, 67·0; H, 6·2; 5OMe, 43·3%). Bargellini and Aureli (*Gazzetta*, 1910, **40**, 346) give m. p. 151° for 2 : 4 : 5 : 3′ : 4′-pentamethoxychalkone.

Hydrolysis of Plathymenin with Alkali.—A solution of plathymenin (1 g.) in 2N-sodium hydroxide (20 c.c.) under nitrogen was heated under reflux for 5 minutes. Acidification precipitated *neo*plathymenin, m. p. after crystallisation, 232° (decomp.) (Found: C, 62·2; H, 4·6%), further characterised by its penta-acetate, m. p. and mixed m. p. 155—156° (Found: C, 60·1; H, 4·9%).

Hydrolysis of O-*Tetramethylplathymenin with Alkali.*—A solution of *O*-tetramethylplathymenin (0·5 g.) in boiling alcohol (100 c.c.), treated with 2N-sodium hydroxide (2 c.c.), deposited when cold 2-hydroxy-4 : 5 : 3′ : 4′-tetramethoxychalkone, *O*-tetramethyl*neo*plathymenin, crystallising from methanol in orange plates, m. p. 174—175°, and having a brown ferric reaction (Found: C, 66·7; H, 5·9; OMe, 35·9. Calc. for $C_{19}H_{20}O_6$: C, 66·3; H, 5·85; 4OMe, 36·1%). Bargellini and Marini-Bettolo (*loc. cit.*) record m. p. 152°. Acetic anhydride–sodium acetate gave 2-*acetoxy*-4 : 5 : 3′ : 4′-*tetramethoxychalkone*, yellow needles, m. p. 118—119°, from aqueous methanol (Found: C, 65·0; H, 5·8. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%).

Oxidation of neo*Plathymenin* 4 : 5 : 3′ : 4′-*Tetramethyl Ether.*—(a) *With potassium permanganate.* The chalkone (1 g.) was treated in acetone solution with potassium permanganate until the reaction slackened. The mixture obtained by addition of water (20 c.c.) and distillation of the acetone was saturated with sulphur dioxide, and the solution extracted with ether. The

mixed acids removed from the ethereal solution with aqueous sodium hydrogen carbonate were treated with diazomethane. From the product 2N-sodium hydroxide extracted methyl 2-hydroxy-4 : 5-dimethoxybenzoate, which, when sublimed under low pressure and crystallised from aqueous methanol, formed needles (0·14 g.), m. p. 94—94·5° (lit., 95°) (Found : C, 56·4; H, 5·6. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%). The acid obtained by alkaline hydrolysis had m. p. 204° (lit., from 203° to 213°) (Found : C, 54·1; H, 5·1. Calc. for $C_9H_{10}O_5$: C, 54·5; H, 5·1%). Both acid and ester gave a bright blue ferric colour.

The alkali-insoluble ester, purified by distillation, consisted of methyl veratrate, m. p. and mixed m. p. 59—60°.

(b) *With hydrogen peroxide.* To the tetramethylchalkone (0·1 g.) dissolved in warm N-sodium hydroxide (40 c.c.), 30% hydrogen peroxide (2 c.c.) was added. 3-Hydroxy-6 : 7 : 3′ : 4′-tetramethoxyflavone separated in the cold and crystallised from aqueous methanol in yellow plates, m. p. 226° (Found : C, 63·5; H, 5·2; OMe, 34·0. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·1; 4OMe, 34·6%). Bargellini and Marini-Bettolo (*loc. cit.*) found m. p. 228°.

6 : 7 : 3′ : 4′-*Tetramethoxyflavone.*—*O*-Tetramethylplathymenin (1 g.) was heated with selenium dioxide (0·5 g.) under reflux in *iso*amyl alcohol (20 c.c.). The product which was deposited in the cold was separated from selenium by recrystallisation, 6 : 7 : 3′ : 4′-tetramethoxyflavone being obtained as long needles, m. p. 215—216° (lit., 219°), from methanol (Found : C, 66·8; H, 5·4; OMe, 35·9. Calc. for $C_{19}H_{18}O_6$: C, 66·7; H, 5·3; 4OMe, 36·2%).

The award (to K. G. N.) by the Directors of Messrs. British Celanese, Ltd., of a research studentship is gratefully acknowledged.

THE UNIVERSITY, NOTTINGHAM. [*Received, December 18th,* 1952.]

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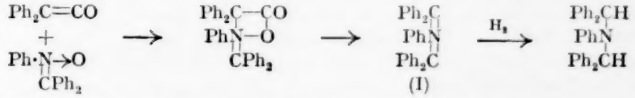
215. *The Structure of the Nitrenes.*

By C. H. HASSALL and A. E. LIPPMAN.

It has been established by degradation and synthesis that nitrenes (Staudinger and Miescher, *Helv. Chim. Acta*, 1919, **2**, 564) should be formulated as *o*-diphenylmethylphenylimino-derivatives. The structure and formation of the precursors of nitrenes, addition products obtained on interaction of *N*-phenylnitrones and diphenylketen, have been discussed.

IN studies on the interaction of diphenylketen and various anil *N*-oxides (nitrones), Staudinger and Miescher (*Helv. Chim. Acta*, 1919, **2**, 564) found that *N*-phenylnitrones gave addition compounds which, when heated, decomposed to carbon dioxide and what appeared to be a novel type of product, termed nitrenes. The following course of reaction was proposed :



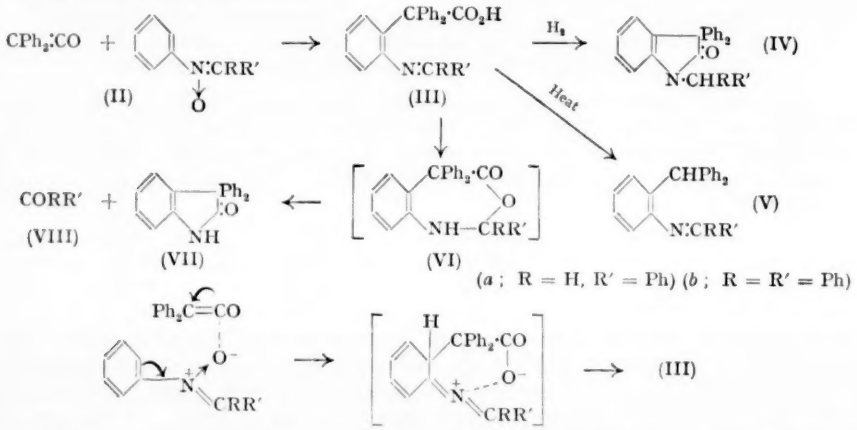
It was suggested that the nitrene structure (I) accounted for the yellow colour and for the addition of halogens, halogen acids, and hydrogen. In the case of pentaphenylnitrene (I) the dihydro-derivative appeared identical with a product obtained in small yield by heating *N*-diphenylmethylaniline with diphenylmethyl bromide. It did not give a nitroso-derivative.

As the quinquecovalent formulation (I) appeared untenable, further investigations were undertaken by Taylor, Owen, and Whittaker (*J.*, 1938, 207), whose evidence led them to an ethyleneimine structure. " Triphenyl-*N*-phenylnitrene," prepared from benzaldoxime *N*-phenyl ether (benzylideneaniline oxide) (II), was obtained colourless. The single product, m. p. 152°, obtained by reduction with aluminium amalgam, gave a nitroso-derivative. The following reactions were suggested :

We have now obtained evidence, from studies on triphenyl-*N*-phenylnitrene and pentaphenylnitrene, which refutes the ethyleneimine formulation. Catalytic hydrogenation of triphenyl-*N*-phenylnitrene gave a single dihydro-compound, m. p. 160—161°; but aluminium amalgam (Taylor, Owen, and Whittaker, *loc. cit.*) gave three products, m. p.s 242°, 160°, and 125°, the principal component being identical with the product of catalytic hydrogenation. Direct comparison showed that these compounds all differed from the two possible reduction products of the ethyleneimine structure, *viz.*, 1-anilino-1 : 2 : 2-triphenylethane (Bergman and Rosenthal, *J. pr. Chem.*, 1933, **135**, 267) and 1-anilino-1 : 1 : 2-triphenylethane prepared by condensation of benzophenone anil with benzylsodium.

It appeared to us that, of the possible modes of reaction of diphenylketen with nitrones, that involving substitution in the *N*-phenyl nucleus was favoured by the observation of the earlier workers that when hydrogen or aliphatic radicals replaced this grouping no nitrene could be obtained. We obtained further support for this view by identifying as 3 : 3-diphenyloxindole the product regularly isolated from the mother-liquors after the interaction of diphenylketen and the *N*-phenylnitrone (Staudinger and Miescher, *loc. cit.*). This compound is also readily obtained, together with benzaldehyde or benzophenone, when the addition products from the *N*-phenyl ethers of benzaldoxime and benzophenone oxime respectively are dissolved in concentrated sulphuric acid or heated in acetic acid or ethanol.

This suggested the possibility of formulating nitrenes as *o*-diphenylmethylphenylimino-derivatives (*o*-$CHPh_2 \cdot C_6H_4 \cdot N{=}$), which was supported by the similarity of the ultra-violet absorption spectrum of pentaphenylnitrene and benzophenone anil and confirmed by synthesis and by acid hydrolysis to *o*-aminophenyldiphenylmethane. The dihydro-derivative of triphenyl-*N*-phenylnitrene was identified as *o*-benzylaminophenyldiphenyl-methane, *o*-$CHPh_2 \cdot C_6H_4 \cdot NH \cdot CH_2Ph$, by comparison with synthetic material. No nitroso- or acetyl derivative of *o*-diphenylmethylaminophenyldiphenylmethane could be prepared, in agreement with Staudinger and Miescher's observation which led them however to regard this compound as a tertiary amine.



The addition products which are precursors of the nitrenes contain one active hydrogen atom and, on hydrogenation, absorb one mol. of hydrogen with loss of an atom of oxygen. The infra-red absorption spectra of these reduction products closely resemble that of 3 : 3-diphenyloxindole : carbonyl absorption at 5·83 μ, typical of carbonyl groups in similar five-membered rings (Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 1289), is present in all of them, but a band at 3·0 μ due to the NH stretching vibration only appears in 3 : 3-diphenyloxindole. Thus the nitrogen atom in the reduction product is tertiary (Randall, Fowler, Fuson, and Dangl, "Infra Red. Determination of Organic Structures," Van Nostrand, New York, 1949). 1-Benzyl-3 : 3-diphenyloxindole, prepared by benzylation of 3 : 3-diphenyloxindole, is identical with the reduction product of the adduct obtained from benzaldoxime *N*-phenyl ether. The evidence favours the formulation of

the addition products as derivatives (III) of *o*-aminophenyldiphenylacetic acid. This structure accounts for reduction to a substituted oxindole (IV) (cf. reduction of *o*-nitrophenylacetic acid to oxindole, Bayer, *Ber.*, 1878, **11**, 583), formation of a compound (V) by decarboxylation, and decomposition to 3 : 3-diphenyloxindole (VII). The last reaction is interpreted as proceeding by way of the lactone (VI) which decomposes to (VII) and (VIII). This decomposition would be analogous to, *inter al.*, the hydrolysis of derivatives of benzylideneanthranilic acid (Snyder, Levin, and Wiley, *J. Amer. Chem. Soc.*, 1938, **60**, 2025) and of benzylideneglycine (Bergman, Eusslin, and Zervas, *Ber.*, 1925, **58**, 1034). It is doubtless facilitated by the strong tendency for formation of the oxindole ring. We consider that the similarity of the ultra-violet absorption spectrum to that of the corresponding nitrene and the ease of formation of the water-insoluble monosodium salt favours the formulation of the primary addition product as (III) rather than as (VIII) which could also account for the reaction products obtained. This does not, however, exclude the possibility of an equilibrium mixture containing a proportion of the lactone form, as has been suggested for benzylideneanthranilic acid (Snyder, Levin, and Wiley, *loc. cit.*).

The course of reaction of diphenylketen with an *N*-phenylnitrone is suggested by the structure of the addition product. It appears that the electrophilic character of the nitrogen atom has been transmitted to the *N*-phenyl nucleus, so that the diphenylmethylidene group becomes attached to the *ortho*-position. This is followed by a prototropic change to (III). Although this is in keeping with the known properties of ketens (Staudinger, "Die Ketene," Enke, Stuttgart, 1912) it is an exceptional mode of reaction for nitrones which normally undergo 1 : 3-addition (Smith, *Chem. Reviews*, 1938, **23**, 229).

Experimental

Ultra-violet absorption spectra were obtained with a Beckman D.U. Spectrophotometer. Infra-red absorption spectra were determined with a Baird Associates instrument by Dr. S. M. Nagy, Massachusetts Institute of Technology.

1-*Anilino*-1 : 1 : 2-*triphenylethane*.—This was not obtained on condensation of aniline under forcing conditions with 1 : 1 : 2-triphenylethanol or 1-chloro-1 : 1 : 2-triphenylethane or Clemmensen reduction of α-benzoyldiphenylmethylaniline.

Benzylsodium (Gilman, Pacevitz, and Baine, *J. Amer. Chem. Soc.*, 1940, **62**, 1518) [from sodium (5·75 g.) and chlorobenzene (11·25 g.)] reacted readily with benzophenone anil (13·0 g., 0·05 mol.). The mixture was heated under reflux for 1 hour, treated with ethanol to destroy excess of sodium, and poured into water. The toluene layer was dried and distilled *in vacuo*. The residual *amine* crystallised from ethanol as light brown needles, m. p. 142—143° (7·3 g., 41%) (Found : C, 89·4; H, 6·5; N, 4·0. $C_{26}H_{23}N$ requires C, 89·5; H, 6·6; N, 4·1%).

Attempted Synthesis of Triphenyl-N-phenylethyleneimine.—α-Benzoyldiphenylmethylaniline (Cameron, *Trans. R. Soc. Canada*, 1929, 53) (198 mg., 0·54 millimole) in anhydrous ether (25 c.c.) was refluxed with lithium aluminium hydride (268 mg., 7·4 millimole) for 5 hours. The excess of reagent was decomposed with water. 2-*Anilino*-1 : 2 : 2-*triphenylethanol* crystallised from ethanol as prisms (crude yield, 103 mg., 50%), m. p. 176—178° (Found : C, 85·4; H, 6·3; N, 3·8. $C_{26}H_{23}ON$ requires C, 85·5; H, 6·3; N, 3·8%). Attempts to bring about ring closure by heating or by dehydrohalogenation of the chloro-derivative, prepared with thionyl chloride, were not successful.

o-*Benzylideneaminophenyldiphenylmethane* ("*Triphenyl-N-phenylnitrene*").—The addition product, o-*benzylideneaminophenyldiphenylacetic acid* (IIIa), prepared from diphenylketen and benzylideneaniline oxide (II*a*) in 44% yield, had m. p. 185—188° (decomp.) (Found : C, 82·5; H, 5·4; N, 3·6. $C_{27}H_{21}O_2N$ requires C, 82·8; H, 5·4; N, 3·6%).

At 215° this rapidly gave carbon dioxide and the *nitrene* (93%). Crystallisation from ethanol and chromatography in benzene–light petroleum (1 : 1) on activated alumina gave needles, m. p. 104—105° [Found : C, 89·9; H, 6·1%; N, 4·1%; *M* (Rast), 355. $C_{26}H_{21}N$ requires C, 90·0; H, 6·1; N, 4·0%; *M*, 347]. Absorption spectrum in EtOH : $\lambda_{max.}$ 260 (log ε 4·20), and 315 mμ (log ε 3·69).

Hydrolysis. The nitrene (250 mg.) was boiled with 2N-sulphuric acid (5 c.c.) with continuous passage of steam. The distillate yielded benzaldehyde 2 : 4-dinitrophenylhydrazone (97%), m. p. and mixed m. p. 236—238°. The colourless product obtained on neutralisation of the residue in the distillation flask with ammonia was purified by chromatography on activated alumina [50% benzene–light petroleum (b. p. 60—80°); elution, benzene–methanol (9 : 1)] and

recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) needles (Found: C, 88·1; H, 6·5; N, 5·3. Calc. for $C_{19}H_{17}N$: C, 88·0; H, 6·6; N, 5·4%), m. p. and mixed m. p. with authentic *o*-aminophenyldiphenylmethane, 127—128°. It gave an acetyl derivative, m. p. and mixed m. p. 152—155°.

Reduction. (*a*) The nitrene (1·43 g.) was kept with amalgamated aluminium (from 2 g. of aluminium turnings) in moist ether (50 c.c.) at room temperature for 48 hours, then filtered off, and the insoluble material extracted with ether. The pale yellow oil obtained after removal of solvent was chromatographed in benzene on alumina (35 g.). The main product was eluted with benzene and separated by fractional crystallisation into fractions, m. p. 200—210° (289 mg.) and 138—148° (588 mg.). The former on further chromatography and several recrystallisations from ethyl acetate–methanol gave a product, m. p. 242—244°. Insufficient was available to complete the purification.

The low-melting fraction was chromatographed on alumina (Spence Type H; 25 g.). Elution with benzene–light petroleum gave material (268 mg.), fluorescing blue in ultra-violet light, and giving on recrystallisation from ethyl acetate–light petroleum the product (m. p. 160—161°) obtained also on hydrogenation (see below). Benzene containing 1% of ethyl acetate removed non-fluorescent material (221 mg.) which on crystallisation from aqueous alcohol afforded *o*-aminophenyldiphenylmethane, m. p. and mixed m. p. 125—127°.

(*b*) The nitrene (1·985 g.) in ethanol (200 c.c.) was hydrogenated (1·14 mols.) at 1 atm. with Adams's platinum catalyst. The product crystallised from ethanol as prisms, m. p. 160—161° (Found: C, 89·7; H, 6·7; N, 4·3. Calc. for $C_{26}H_{23}N$: C, 89·4; H, 6·6; N, 4·0%).

o-*Benzylaminophenyldiphenylmethane.*—*o*-Aminophenyldiphenylmethane was refluxed for 1 hour with benzyl chloride. The product had m. p. 160—161° alone or mixed with the foregoing reduction product.

Benzylideneaminophenyldiphenylmethane (V*a*).—*o*-Aminophenyldiphenylmethane (Baeyer and Bassett, *Ber.*, 1904, **37**, 3192) (2·54 g.) was heated with benzaldehyde (2·5 g.) on a water-bath for 1 hour. The *product* crystallised from ethanol as needles, m. p. 104—105° alone or mixed with the "nitrene" (Found: C, 90·2; H, 6·4. $C_{26}H_{21}N$ requires C, 89·9; H, 6·1%).

o-*Diphenylmethyleneaminophenyldiphenylmethane* (*Pentaphenylnitrene*) (V*b*).—When the addition product from *N*-diphenylmethylideneaniline oxide and diphenylketen was heated at 215°, the *diphenylmethylene* compound was obtained in 73% yield as yellow needles, m. p. 136—137° (Found: C, 90·9; H, 5·9; N, 3·3. $C_{32}H_{25}N$ requires C, 90·8; H, 5·95; N, 3·3%). Absorption spectrum in ethanol: $\lambda_{max.}$ 250 (log ε 4·13) and 340 mμ (log ε 3·36).

Hydrolysis of this (620 mg.) with N-sulphuric acid during 10 hours gave *o*-aminophenyldiphenylmethane and benzophenone in good yields.

Reduction of the nitrene with aluminium amalgam or hydrogen–platinum as described above gave only o-*diphenylmethylaminophenyldiphenylmethane*, m. p. 158—159·5° [Found: C, 90·7; H, 6·3; N, 3·2%; *M* (Rast), 423. $C_{32}H_{27}N$ requires C, 90·2; H, 6·35; N, 3·3%; *M*, 425].

o-*Benzylideneaminophenyldiphenylacetic Acid.*—When kept, the acid (III*a*) developed a smell of benzaldehyde and gave a compound $C_{20}H_{15}ON$. This reaction occurs more readily in a solvent such as ethanol, acetic acid, or cold, concentrated sulphuric acid.

When the acid (III*a*) (313 mg.) was refluxed for ½ hour with 2 : 4-dinitrophenylhydrazine sulphate in methanol, a precipitate was obtained on cooling. This was separated by recrystallisation from ethanol into benzaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 241°, and a less soluble fraction, 3 : 3-diphenyloxindole, m. p. and mixed m. p. 228° [Found: C, 84·0; H, 5·4; N, 5·0%; *M* (Rast), 288. Calc. for $C_{20}H_{15}ON$: C, 84·0; H, 5·25; N, 4·9%; *M*, 285]; acetyl derivative, m. p. 176—177° (Found: C, 80·6; H, 5·3; N, 4·2. Calc. for $C_{22}H_{17}O_2N$: C, 80·7; H, 5·2; N, 4·3%) (cf. Wegmann and Dahn, *Helv. Chim. Acta*, 1946, **29**, 429).

The acid (III*a*) (136 mg.), suspended in ethyl acetate (50 c.c.), was shaken with hydrogen in presence of Adams's catalyst until dissolved. The residue obtained on distillation of solvent was recrystallised from aqueous methanol and ethyl acetate–light petroleum as plates, m. p. 161—162° (Found: C, 86·7; H, 5·8; N, 3·65. $C_{27}H_{21}ON$ requires C, 86·4; H, 5·6; N, 3·7%). These were identified as 1-*benzyl*-3 : 3-*diphenyloxindole* (IV*a*) by comparison with a sample prepared by heating benzyl chloride (1 c.c.) with 3 : 3-diphenyloxindole (0·70 g.), sodium (204 mg.), and anhydrous benzyl alcohol (25 c.c.). After 4 hours the solvent and excess of reagents were distilled off and the residue treated with water. The product was extracted with chloroform and recrystallised from ethanol as plates (540 mg.), m. p. and mixed m. p. 160—161° (Found: C, 86·4; H, 5·5; N, 3·9%).

o-Diphenylmethylideneaminophenyldiphenylacetic Acid (III*b*).—This *acid* was obtained as yellow, crystals, m. p. 170—172° (decomp.) by Staudinger and Miescher's method (*loc. cit.*) (Found: C, 84·3; H, 5·47; N, 2·9; active H, 0·28. $C_{33}H_{25}O_2N$ requires C, 84·8; H, 5·4; N, 3·0; 1 H, 0·22%). Absorption spectrum in EtOH: $\lambda_{max.}$ 250 (log ε 4·38) and 355 mμ (log ε 3·62). The similarity of the absorption spectrum of benzophenone anil, $\lambda_{max.}$ 246 (log ε 4·10) and 335 mμ (log ε 3·36), to that of pentaphenylnitrene (V*b*) is an argument in favour of the presence in this acid of a chromophore containing the ⁻C=N⁻ grouping. It is insoluble in water or light petroleum, but somewhat soluble in ethyl acetate, ether, benzene, ethanol, or acetone, and dissolves rapidly in pyridine. It is not soluble in hot aqueous sodium hydroxide or carbonate. When a solution of the acid (268 mg.) in a mixture of N-sodium hydroxide (100 c.c.) and ethanol (100 c.c.) was distilled *in vacuo* at room temperature to remove ethanol a precipitate of *sodium* salt was obtained as a yellow, amorphous powder (279 mg.) (Found: Na, 4·3. $C_{33}H_{24}O_2NNa$ requires Na, 4·8%). Acidification of the aqueous-alcoholic alkaline solution, with cooling, precipitates the original adduct; if the mixture becomes warm, decomposition occurs to 3 : 3-diphenyloxindole.

Decomposition by refluxing with Brady's reagent as described above gave quantitatively 3 : 3-diphenyloxindole and benzophenone 2 : 4-dinitrophenylhydrazone.

Catalytic hydrogenation (uptake, 1·04 mols.) gave 1-*diphenylmethyl*-3 : 3-*diphenyloxindole* as needles, m. p. 219·5—220° (from acetone or ethyl acetate), insoluble in dilute acid or alkali [Found: C, 87·7; H, 5·5; N, 3·0%; *M* (Rast), 411. $C_{33}H_{25}ON$ requires C, 87·8; H, 5·6; N, 3·1%; *M*, 452]. Ultra-violet absorption: $\lambda_{max.}$ 260 mμ (log ε 3·98). The infra-red spectrum is almost identical with that of 1-benzyl-3 : 3-diphenyloxindole.

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216. *Halogenation in the Liquid Phase by Chlorine Trifluoride. The Reaction with Benzene Derivatives and with Carbon Tetrachloride.*

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When chlorine trifluoride reacts with substituted benzene and benzene homologues both substitution and addition of chlorine and fluorine occur, substitution predominating as with benzene (Ellis and Musgrave, *J.*, 1950, 3608). In all cases chlorine substitution is in excess of fluorine substitution but this excess can not be explained by reaction between the chlorine trifluoride and the solvent (carbon tetrachloride) giving the chlorinating agent chlorine monofluoride.

IN an earlier paper (*J.*, 1950, 3608) we discussed the reaction between chlorine trifluoride and benzene in carbon tetrachloride and in the presence of several catalysts. Extension of this work to benzene homologues and derivatives under the same conditions and with cobalt fluoride as catalyst has shown that the percentage substitution in benzene homologues is about the same as for benzene but that, with increase in size of the side chain, the percentage of fluoro-derivative decreases and the amount of unchanged test compound increases. In all cases, about twice as much addition compound was obtained as from benzene. Results for halogenated derivatives of benzene and its homologues showed no correlation. Fluorobenzene alone reacted completely but it gave no trace of difluorobenzene even when precautions were taken to avoid possible causes of decomposition. *p*-Difluorobenzene (Schiemann and Pillarsky, *Ber.*, 1929, **62**, 3041; Dunker and Starkey, *J. Amer. Chem. Soc.*, 1939, **61**, 3005) was quite stable to the other reagents present, but in the presence of chlorine trifluoride and cobaltous fluoride it decomposed almost completely. Thus it probably decomposes as it is formed. This would also account for the somewhat lower yield of other products.

All of the addition compounds except those from benzotrichloride and benzotrifluoride were less stable than those from benzene, and decomposed readily on distillation. Analysis after a single distillation generally showed the addition of one chlorine and one fluorine atom per molecule.

The substitution compounds were all examined in a 38-plate concentric-tube fraction-

ating column (Naragon and Lewis, *Analyt. Chem.*, 1946, **18**, 449) but it was not possible to separate any of the fluoro-derivatives except that from chlorobenzene, since they were generally obtained in small amounts, had boiling points near to those of the test compounds, and distilled with the unchanged test compound or as intermediate fractions. Some chlorofluorobenzene was isolated from chlorobenzene, which, from its refractive index can only have been the *para*-isomer. The greater amounts of chloro-derivatives enabled pure samples of some isomers to be separated and examination of graphs of refractive index of distillate against volume distilled often showed that other isomers could not be present. Wherever possible, confirmation of structure was obtained by conversion of the pure samples into the corresponding benzoic acids, either by oxidation or hydrolysis. In general the results are similar to those of chlorination (Reese, *Chem. Reviews*, 1934, **14**, 55; Wertyporoch, *Annalen*, 1932, **493**, 153; Varma *et al.*, *J. Indian Chem. Soc.*, 1944, **21**, 112).

All of the compounds examined except benzotrichloride gave, as did benzene, a considerably greater proportion of chloro- than fluoro-substitution product. We suggested (*loc. cit.*) that this was probably due to reaction between chlorine trifluoride and the solvent giving the chlorinating agent chlorine monofluoride, although Ruff and Krug (*Z. anorg. Chem.*, 1930, **190**, 270) claim that reaction between the two, even in the liquid state, occurs only on warming. Results have shown (Table, Expts. 1—6) that some reaction occurs even at 0° and increases considerably with rise in temperature but that, when benzene is present (Expts. 7 and 8), the chlorine trifluoride reacts preferentially with it and not at all with the solvent and, even if this were not so, the heat of reaction does not raise the temperature sufficiently for the production of enough chlorine monofluoride. Since in experiments 1—3 the volume of reaction mixture plus products agreed very closely with the initial volume of carbon tetrachloride, there can have been no errors due to incomplete condensation.

Expt.	ClF_3, g.; flow rate, g./hr.	Temp., °c.	CCl_2F_2, ml.	Intermediate fraction, ml.	CCl_3F, ml.	CCl_4 carried over, ml.
1	40; 6	25	0·5	1·0	12·5	16·0
2	42; 5	25	2·1	1·6	16·9	16·5
3	41; 6	0	—	0·5	2·8	6·5
4	43; 6	20	4·2	1·0	13·3	16·0
5	40; 6	25	3·1	—	20·5	22·0
6	42; 6	0	—	0·7	3·9	6·0
7	30; 6	6	—	—	—	6·0
8	65; 10	9	—	—	—	5·9

In all cases the chlorine trifluoride was diluted with nitrogen (5 l./hr.).
In expts. 1—3 there was no catalyst; cobalt fluoride (10 g.) was used in expts. 4—6. In expts. 7 and 8 the carbon tetrachloride contained cobalt fluoride + benzene (100 g.).

Experimental

Halogenation of Benzene Derivatives.—The apparatus and technique were as previously described (Ellis and Musgrave, *loc. cit.*), the test compound (100 g.) in carbon tetrachloride (500 ml.) being stirred with cobalt fluoride (10 g.) and treated at 0° with chlorine trifluoride (0·5 mol.), diluted with nitrogen (12 l./hr.). As before, no free halogen or hydrogen chloride could be detected in the exit gases. The method of working up differed only in that improved filtration and washing of the residues with carbon tetrachloride cut down the overall loss of solvent to 30—40 ml. (previously 50—100 ml.). Each reaction mixture was distilled rapidly under reduced pressure, solid carbon dioxide–ethanol traps being used, to separate solvent and substitution products (*A*) from addition products and tar (*B*) with the minimum decomposition of the latter. The product *A* was then fractionated through a 22-plate column and each fraction refractionated through a 38-plate concentric-tube column [length of concentric tube portion, 32 cm.; outside diameter of inner tube, 6·8 mm.; inside diameter of outer tube, 8·0 mm.; a boil-up rate of 75 drops/min. and a take-off rate of 1 ml./hr. being used]. The efficiency of the column was determined by distilling *n*-heptane–methyl*cyclo*hexane (Lecky and Ewell, *Analyt. Chem.*, 1940, **12**, 547; Bromiley and Quiggle, *Ind. Eng. Chem.*, 1933, **25**, 1136). By using it, pure samples of *o*- and *p*-chlorotoluenes were obtained from 16 ml. of a mixture of equal parts of the two at reduced (14 mm.) as well as atmospheric pressure. It was not as efficient under reduced pressure as at atmospheric pressure but no estimate of the efficiency under reduced pressure was made.

Toluene. Distillation of the washed and dried reaction mixture gave (*A*), b. p. <100°/10 mm., fractionation of which gave: (*a*) Carbon tetrachloride. (*b*) A mixture (27·2 g.) of toluene and fluorotoluene, b. p. 110—117° (19·0 g. of toluene and 8·2 g. of fluorotoluene, by fluorine analysis), separated into toluene (11 ml.), n_D^{20} 1·4966—1·4955, intermediate fraction (14 ml.), n_D^{20} 1·4948—1·4755, and fluorotoluenes (3·5 ml.), n_D^{20} 1·4743—1·4715 (Found, in specimen from last ml.; F, 17·1. Calc. for C_7H_7F: F, 17·3%) [oxidation with permanganate gave a mixture of fluorobenzoic acids (40%), m. p. 158°]. (*c*) Benzyl fluoride (1·8 g.), b. p. 38—39°/12 mm., which after redistillation (1 g.) had b. p. 139°, n_D^{20} 1·4916 (Found: F, 17·1%) [oxidation with permanganate gave benzoic acid (75%), m. p. and mixed m. p. 122°]. (*d*) Chlorotoluenes (22·1 g.), b. p. 52—57°/12 mm., separated into (i) *o*-chlorotoluene (4 ml.), b. p. 159°, n_D^{20} 1·5261 (Found: Cl, 27·9. Calc. for C_7H_7Cl: Cl, 28·1%) [oxidation gave *o*-chlorobenzoic acid (68%), m. p. and mixed m. p. 141°]; (ii) intermediate fraction (11 ml.), n_D^{20} 1·5258—1·5213; and (iii) *p*-chlorotoluene (4·5 ml.), b. p. 162°, n_D^{20} 1·5211 (Found: Cl, 28·0%) [oxidation gave *p*-chlorobenzoic acid (75%), m. p. and mixed m. p. 241°]. *m*-Chlorotoluene must be absent since it would distil with the *para*-isomer and affect its physical constants. (*e*) Residue (addition compounds) (3·7 g.).

The residue (*B*; 33 g.) left after removal of (*A*) gave: (i) a viscous oil (20·1 g.), b. p. 100—160°/10 mm., which decolorised aqueous permanganate and bromine water and decomposed when kept (Found: Cl, 23·5; F, 12·8. Calc. for C_7H_8ClF: Cl, 24·2; F, 13·0%), and (ii) a tarry residue (12·9 g.).

Ethylbenzene. Fractionation of (*A*), b. p. <85°/10 mm. gave: (*a*) carbon tetrachloride. (*b*) Ethylbenzene (19 ml.), b. p. 136°, n_D^{20} 1·4957—1·4945. (*c*) A mixture (14 ml.) of ethylbenzene and ethylfluorobenzenes (3·7 g. by analysis), b. p. 137—140°, n_D^{20} 1·4943—1·4792. (*d*) *o*-Chloroethylbenzene (4 ml.), b. p. 179·5°, n_D^{20} 1·5214 (Found: Cl, 25·2. Calc. for C_8H_9Cl: 25·3%) [oxidation gave *o*-chlorobenzoic acid (55%), m. p. and mixed m. p. 141°]. (*e*) *o*- and *p*-(and possibly some *m*-)chloroethylbenzenes (6 ml.), n_D^{20} 1·5211—1·5180. (*f*) *p*-Chloroethylbenzene (6 ml.), b. p. 184·5, n_D^{20} 1·5175 (Found: Cl, 25·2%) [oxidation gave *p*-chlorobenzoic acid (65%), m. p. and mixed m. p. 241°].

The residue (*B*; 28 g.) after distillation of (*A*) gave: (i) unstable addition compounds (12·7 g.), b. p. 85—125°/10 mm., which decolorised aqueous permanganate and bromine water (Found: Cl, 24·0; F, 11·2. Calc. for $C_8H_{10}ClF$: Cl, 22·1; F, 11·8%), and (ii) tar (14·8 g.).

Cumene. Fractionation of (*A*), b. p. <88°/8 mm. gave: (*a*) Carbon tetrachloride. (*b*) Cumene (35 ml.), b. p. 152°, n_D^{20} 1·4910—1·4895. (*c*) A mixture (12 ml.) of cumene and fluorocumenes, b. p. 153—156°, n_D^{20} 1·4893—1·4828 [containing fluorocumenes (2·8 g.)]. (*d*) *p*-Chlorocumene (18·5 ml.), b. p. 82°/15 mm., n_D^{20} 1·5120 (Found: Cl, 23·1. Calc. for $C_9H_{11}Cl$: Cl, 23·0%) [oxidation (difficult) gave *p*-chlorobenzoic acid (25%), m. p. and mixed m. p. 241°].

The residue (*B*; 22·1 g.) gave: (i) unstable addition compounds (10·6 g.), b. p. 88—110°/8 mm., which decolorised aqueous permanganate and bromine water (Found: Cl, 22·6; F, 10·1. Calc. for $C_9H_{12}ClF$: Cl, 20·3; F, 10·9%), and (ii) tar (11·5 g.).

Chlorobenzene. Fraction (*A*), b. p. <88°/8 mm. gave: (*a*) Carbon tetrachloride. (*b*) *p*-Chlorofluorobenzene (1·5 ml.), b. p. 129·8/754 mm., n_D^{20} 1·4967—1·4973 (Found: Cl, 27·4; F, 14·4. Calc. for C_6H_4ClF: Cl, 27·2; F, 14·55%). (*c*) A mixture (14 ml.) of chlorobenzene and *p*-chlorofluorobenzene, n_D^{20} 1·4973—1·5237. (*d*) Chlorobenzene (1 ml.), b. p. 132°, n_D^{20} 1·5243 (Found: Cl, 31·4. Calc. for C_6H_5Cl: Cl, 31·55%).

Separation of fractions (*b*), (*c*), and (*d*) required three distillations through the concentric-tube column, *o*-dichlorobenzene (4 ml.) being used as chaser for the chlorobenzene. The boiling point and refractive index indicated that *o*- and *m*-chlorofluorobenzene could only be present in minute amounts, if at all. The bulked fractions before distillation contained 17·8 g. of chlorofluorobenzene and 14·9 g. of chlorobenzene (Found: Cl, 29·2; F, 7·95%), and were quite stable to aqueous permanganate and bromine water.

(*e*) *p*-Dichlorobenzene (38·7 g.), b. p. 62°/10 mm., m. p. and mixed m. p. 53° (Found: Cl, 48·3. Calc. for $C_6H_4Cl_2$: Cl, 48·3%). (*f*) *o*-Dichlorobenzene (2·1 g.), b. p. 69°/10 mm., 180°/755 mm., n_D^{20} 1·5511, f. p. −15·5°, mixed f. p. −16° (Found: Cl, 48·2%).

The residue (*B*; 11·6 g.) gave: (i) addition compounds (2·5 g.), b. p. 88—92°/8 mm., n_D^{20} 1·5172, which decolorised aqueous permanganate and bromine water (Found: Cl, 46·3; F, 13·2. Calc. for $C_6H_5Cl_2F$: Cl, 42·6; F, 11·4%), and (ii) tar (9·1 g.).

Fluorobenzene. Fractionation of (*A*), b. p. <63°/10 mm., gave: (*a*) Carbon tetrachloride (no fluorine could be detected in any of several samples analysed). (*b*) *p*-Chlorofluorobenzene (27 g.), b. p. 130°, n_D^{20} 1·4965 (Found: Cl, 27·0; F, 14·7. Calc. for C_6H_4ClF: Cl, 27·2; F, 14·55%). (*c*) Residue (2·6 g.).

The residue (*B*; 19·7 g.) gave: (i) addition products (2·4 g.), b. p. 63—67°/19 mm., n_D^{20} 1·4652 (Found: Cl, 27·1; F, 23·0%), which decolorised aqueous permanganate and bromine water; (ii) addition products (9·7 g.), b. p. 90—135°/10 mm., n_D^{20} 1·5153 (Found: Cl, 21·2; F, 26·4. Calc. for $C_6H_5ClF_2$: Cl, 17·7; F, 38·0%); and (iii) tar (7·6 g.).

A similar experiment, on half-scale, in which the mixture was neutralised with potassium fluoride (solid) and was never allowed to come into contact with aqueous reagents gave: (*a*) Carbon tetrachloride (approx. 200 ml.), containing less than 1% of fluorine; (*b*) *p*-chlorofluorobenzene (11·2 g.), b. p. 130°; (*c*) residue (2·8 g.); (*d*) addition compounds (4·8 g.), b. p. 60—140°/8 mm.; and (*e*) tar (4·5 g.).

Benzotrifluoride. (*A*), b. p. <63°/14 mm., gave: (*a*) Carbon tetrachloride. (*b*) A mixture (21·4 g.) of benzotrifluoride and ααα-tetrafluorotoluene (13·2 g. and 8·2 g., respectively, by fluorine analysis), b. p. 102·5°, n_D^{20} 1·4076, which distilled unchanged through the concentric-tube column. (*c*) *m*-Chlorobenzotrifluoride (26·2 g.), b. p. 138·5°, n_D^{20} 1·4467 (Found: Cl, 19·5; F, 31·7. Calc. for $C_7H_4ClF_3$: Cl, 19·7; F, 31·6%) [hydrolysis with 80% sulphuric acid gave *m*-chlorobenzoic acid (51%), m. p. and mixed m. p. 156°].

The residue (*B*; 19·9 g.) gave: (i) addition products (10·6 g.), b. p. 63—88°/14 mm., n_D^{20} 1·4352 (Found: Cl, 18·1; F, 37·6. Calc. for $C_7H_5ClF_4$: Cl, 17·7; F, 37·95%), which decolorised aqueous permanganate and bromine water; and (ii) tar (9·3 g.).

Benzotrichloride. (*A*), b. p. <145°/10 mm., gave: (*a*) Carbon tetrachloride. (*b*) αα-Dichloro-α-fluorotoluene (1·2 g.), b. p. 65°/8 mm., 178°, n_D^{20} 1·5170 (Found: Cl, 39·6; F, 10·7. Calc. for $C_7H_5Cl_2F$: Cl, 39·7; F, 10·6%) [hydrolysis with concentrated sulphuric acid at 70° for 30 minutes gave benzoic acid (69%), m. p. and mixed m. p. 122°]. (*c*) A mixture (53 g.) of benzotrichloride and fluorobenzotrichloride, b. p. 100·5/15 mm., n_D^{20} 1·5507, which did not separate during distillation. Analysis (Found: Cl, 52·4; F, 2·6%) showed the mixture to contain fluorobenzotrichloride (15·4 g.) and benzotrichloride (37·6 g.). (*d*) Chlorobenzotrichlorides (17 g.), b. p. 125°/15 mm., n_D^{20} 1·5717, which did not separate during distillation (Found: Cl, 61·6. Calc. for $C_7H_4Cl_4$: Cl, 61·7%) [Hydrolysis with water and calcium carbonate (Schiemann and Baumgarten, *Ber.*, 1937, **70**, 1419) gave a mixture of chlorobenzoic acids (60%), m. p. 146° (Found: Cl, 22·6. Calc. for $C_7H_5O_2Cl$: Cl, 22·7%)].

The residue (*B*; 14·6 g.) gave: (i) addition products (11·2 g.), b. p. 145—155°/10 mm., n_D^{20} 1·5352 (Found: Cl, 54·2; F, 13·0. Calc. for $C_7H_5Cl_4F$: Cl, 56·8; F, 7·6); and (ii) tar 3·4 g.).

The Stability of p-*Difluorobenzene.*—*p*-Difluorobenzene (2·3 g.), b. p. 89°, n_D^{20} 1·4420 (Schiemann and Pillarsky, *Ber.*, 1929, **62**, 3041; Dunker and Starkey, *J. Amer. Chem. Soc.*, 1939, **61**, 3005), was dissolved in carbon tetrachloride (80 g.) and shaken for several hours with (*a*) saturated aqueous sodium hydrogen carbonate (25 ml.) or (*b*) 0·1N-sodium hydroxide (25 ml.); no fluoride ion appeared in the aqueous layer. The organic layer, after being washed with water until neutral and dried ($MgSO_4$), distilled constantly at 77·4°, and analysis in each case (Found: Cl, 89·5%) confirmed that no reaction had occurred.

Similarly, when the azeotrope (5 ml.) was saturated with either anhydrous hydrogen chloride or anhydrous hydrogen fluoride and shaken at 20° for 1 hour, analysis (Found: Cl, 89·4%, in each case) showed that no reaction had occurred.

Reaction with Chlorine Trifluoride.—Chlorine trifluoride (6 g., 0·5 mol.), diluted with nitrogen (12 l./hr.), was passed during 1¼ hours into an ice–water-cooled solution of *p*-difluorobenzene (14 g.) in carbon tetrachloride (150 ml.), containing cobalt fluoride (2 g.). Hydrogen fluoride was evolved but no hydrogen chloride or chlorine. The mixture was washed with saturated aqueous sodium hydrogen carbonate and then with water until neutral, and then dried ($MgSO_4$). Fractionation gave: (i) carbon tetrachloride (fluorine test negative) and (ii) a residue (0·42 g.), which decolorised aqueous permanganate (Found: Cl, 26·35; F, 11·35%). Thus almost complete decomposition of the difluorobenzene had occurred.

Reaction between Chlorine Trifluoride and Carbon Tetrachloride.—In the uncatalysed experiments (Table, 1—3) dry carbon tetrachloride (500 ml.) was treated with chlorine trifluoride, the products were passed through alkaline sodium sulphite solution [$Na_2SO_3,7H_2O$ (252 g.), NaOH (80 g.), in 1 l. water] to remove halogens (Emeléus *et al.*, *J.*, 1948, 2188), and then through two glass traps, one cooled in carbon dioxide–ethanol and the other in liquid oxygen. The contents of these traps were distilled into a low-temperature fractionating column (Ramler and Simons, *Ind. Eng. Chem. Anal.*, 1930, **10**, 648), which was capable of separating methyl chloride and methyl bromide.

In the catalysed experiments a stirrer was introduced through a carbon tetrachloride seal and, to restrict flow resistance, the volume of alkaline sulphite solution was reduced but it was

renewed four times in each experiment. The use of benzene in experiments 7 and 8 made it possible to use a stirrer with a mercury seal and, in order to make the reaction conditions identical with those of experiments 1—6, the exit gases were also bubbled through alkaline sulphite solution. In all cases the products were distilled from the low-temperature still and three fractions were collected: (i) Dichlorodifluoromethane, b. p. −28° to −26°, which was redried ($MgSO_4$) and redistilled (Found: Cl, 58·9; F, 31·2. Calc. for CCl_2F_2: Cl, 58·7; F, 31·4%); (ii) intermediate fraction, b. p. −26° to 23°; and (iii) trichlorofluoromethane, b. p. 23—25°. This also was redried ($MgSO_4$) and redistilled (Found: Cl, 77·7; F, 13·6. Calc. for CCl_3F: Cl, 77·45; F, 13·8%).

One of us (J. F. E.) thanks the Durham Colleges in the University of Durham and the Durham County Education Committee for scholarships.

THE UNIVERSITY, SOUTH ROAD, DURHAM. [*Received, November 26th*, 1952.]

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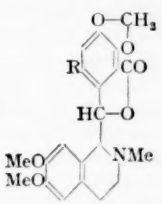
217. *The Synthesis and Resolution of (±)-Corlumine.*

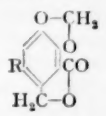
By WILSON M. WHALEY and MORTON MEADOW.

The synthesis of the 3-1′-*iso*quinolylphthalide alkaloid, corlumine (I; R = H) has been completed. Reduction of iodo-(±)-corlumine and deamination of amino-(±)-corlumine afforded (±)-corlumine which was readily resolved by crystallization of the (+)-(hydrogen tartrates) from methanol. The enantiomorphs were identified and compared with naturally occurring (+)-corlumine. No products having the adlumine configuration were encountered.

(±)-ADLUMINE (Manske, *Canadian J. Res.*, 1933, **8**, 210, 404; 1938, **16**, *B*, 81; 1939, **17**, *B*, 51) and (+)-corlumine (Manske, *ibid.*, 1936, **14**, *B*, 325, 347; 1938, 16, *B*, 81; 1940, **18**, *B*, 288) are two of the many alkaloids isolated from certain Fumariaceae. Their structural identity was placed beyond doubt (Manske, *ibid.*, 1933, **8**, 404; 1936, **14**, *B*, 325, 347; 1938, **16**, *B*, 81) by hydrolytic oxidation with dilute nitric acid, lodal and 6-formyl-2 : 3-methylenedioxybenzoic acid being obtained in each case and their identity established by a Cannizzaro rearrangement. No depressions in melting point occurred when the compounds obtained from (+)-corlumine were mixed with the corresponding ones obtained from (+)- and (−)-adlumine. Procedures used by Manske (*loc. cit.*) for the hydrolytic oxidation of adlumine were followed without modification for corlumine. It was obvious, therefore, that the two alkaloids differ only in the disposition of the substituents about the two asymmetric carbon atoms, formula (I; R = H) applying to both bases.



(I)



(II)

Groenewoud and Robinson (*J.*, 1936, 199) synthesized a base which they termed amino-*x*-adlumine *; conversion of the amino-compound into the free base, and resolution and identification of the enantiomorphs have now been accomplished. Their compound is actually amino-(±)-corlumine.

The synthesis followed the methods set forth by Hope and Robinson (*Proc.*, 1910, **26**, 228; *J.*, 1911, **99**, 1153) and Hope, Pyman, Remfry, and Robinson (*J.*, 1931, 236). 6 : 7-Methylenedioxyphthalide (II; R = H) was prepared from *o*-veratraldehyde as described by Perkin and Trikojus (*J.*, 1926, 2925). It was readily nitrated (Groenewoud and Robinson, *loc. cit.*) and the condensation of the 4-nitro-compound with lodal in boiling alcohol

* The *x* signifies that the allocation to the stereoisomeric series α and β had not then been carried out.

followed the usual course. Lodal (Pyman, *J.*, 1909, **95**, 1266) was prepared from homoveratrylamine by a series of reactions involving methods employed by Späth and Polgar (*Monatsh.*, 1929, **51**, 195), Späth and Epstein (*Ber.*, 1926, **59**, 2796), Buck and Ide (*J. Amer. Chem. Soc.*, 1938, **60**, 2102), and Leonard and Leubner (*ibid.*, 1949, **71**, 3410).

It is noteworthy that no condensation occurred between lodal and 4-bromo-6 : 7-methylenedioxyphthalide (II; R = Br) even after extended periods under the usual conditions.

Whereas Groenewoud and Robinson (*loc. cit.*) reduced their nitrated base chemically, catalytic reduction is preferred as it permits easier isolation of the amino-base (I; R = NH_2). The latter was deaminated by two routes. One involved the conversion of the amino-base into the corresponding iodo-compound, followed by catalytic reduction of the latter, while the second method was a direct deamination of the diazotized amine with hypophosphorous acid. The two methods were equally efficacious, identical yields of identical products being obtained.

The (±)-corlumine so obtained has been completely resolved by crystallization of the (+)-(hydrogen tartrates) from methanol; one component is identical with natural (+)-corlumine.

The condensation of lodal with 6 : 7-methylenedioxy-4-nitrophthalide is apparently stereo-selective. Though a mixture of nitro-(±)-adlumine and nitro-(±)-corlumine is to be expected from the condensation, only the nitro-(±)-corlumine was isolated, and that in such a yield (85%) as to preclude a random reaction.

Experimental

M. p.s were determined with a calibrated apparatus. Microanalyses are by Galbraith Laboratories, Knoxville, Tennessee.

6 : 7-*Methylenedioxyphthalide* (II; R = H).—Prepared according to Perkin and Trikojus's method (*loc. cit.*) this compound had m. p. 230—232°. Perkin and Trikojus (*loc. cit.*) gave m. p. 227°, which was confirmed by Späth and Holter (*Ber.*, 1927, **60**, 1897) and Chakravarti (*J. Indian Chem. Soc.*, 1943, **20**, 384). Manske (*Canadian J. Res.*, 1933, **8**, 144) and Groenewoud and Robinson (*loc. cit.*) attributed m. p. 234° and m. p. 233—234°, respectively, to the phthalide.

6 : 7-*Methylenedioxy*-4-*nitrophthalide* (II; R = NO_2).—6 : 7-Methylenedioxyphthalide was nitrated according to Groenewoud and Robinson (*loc. cit.*), who reported m. p. 222—223°. The nitrophthalide obtained had m. p. 230—232°, depressed to 190—192° on admixture with 6 : 7-methylenedioxyphthalide.

4-*Bromo*-6 : 7-*methylenedioxyphthalide* (II; R = Br).—Groenewoud and Robinson (*loc. cit.*) prepared this compound from bromonormeconin, but we preferred to brominate 6 : 7-methylenedioxyphthalide directly. 6 : 7-Methylenedioxyphthalide (1 g.) was heated under reflux for 30 minutes with glacial acetic acid (35 c.c.) and bromine (1 g.). Dilution with ice–water (100 c.c.) induced immediate precipitation. The collected yellow solid was washed with cold alcohol (5 c.c.) and crystallized from ethyl acetate (charcoal). The bromo-compound (0·42 g., 30%) crystallized in long, flat, yellow needles, m. p. 198—199° (Found : C, 42·1; H, 2·0. Calc. for $C_9H_5O_4Br$: C, 42·1; H, 2·1%). Groenewoud and Robinson (*loc. cit.*) reported m. p. 196°.

Under the usual conditions, 4-bromo-6 : 7-methylenedioxyphthalide did not condense with lodal even after extended periods of heating, starting material being recovered in all cases.

4-*Iodo*-6 : 7-*methylenedioxyphthalide* (II; R = I).—A solution of 6 : 7-methylenedioxyphthalide (1 g.) in glacial acetic acid (30 c.c.) was refluxed for 2 hours with iodine monochloride (9·5 g.). After dilution of the solution with water (50 c.c.), the iodine liberated was reduced by sulphurous acid and **4-*iodo*-6 : 7-*methylenedioxyphthalide*** collected (0·27 g., 15%) and washed with cold absolute alcohol (5 c.c.); it formed short, pale-yellow needles, m. p. 192—193° [from ethyl acetate (charcoal)] (Found : C, 35·7; H, 1·7. $C_9H_5O_4I$ requires C, 35·6; H, 1·7%). As a consequence of the low yield, condensation of the iodophthalide with lodal was not attempted.

Lodal.—Lodal was prepared by the treatment of 3 : 4-dihydro-6 : 7-dimethoxy-2-methyl-*iso*quinolinium iodide with aqueous sodium hydroxide (Leonard and Leubner, *loc. cit.*) followed by extraction of the hydroxy-amine with chloroform. Removal of the chloroform in a stream of dry nitrogen afforded lodal. The substituted dihydro*iso*quinolinium iodide was prepared according to the following sequence of reactions :

(a) *N*-3 : 4-*Dimethoxyphenylethylformamide*. 2-(3 : 4-Dimethoxyphenyl)ethylamine (90 g.) and 90% formic acid (35 g.) were heated at 170° for 5 hours and the product (95 g., 91%) distilled; it had b. p. 208—210°/2—3 mm. Späth and Polgar (*loc. cit.*) reported b. p. 170°/0·01 mm.

(b) 3 : 4-*Dihydro*-6 : 7-*dimethoxy*isoquinoline. Cyclization of the formamide was accomplished by refluxing it (19·6 g.) with phosphorus oxychloride (143 g.) and dry toluene (370 c.c.) for 2 hours. The mixture was worked up in the usual manner (Whaley and Govindachari, "Organic Reactions," 1951, **6**, 74); the orange residue distilled at 150—156°/2—3 mm., giving a colourless oil (10·8 g., 61%). Späth and Epstein (*loc. cit.*) used phosphoric oxide as the cyclizing agent and obtained a product, b. p. 155—160°/1 mm.

(c) 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinolinium *iodide*. The methiodide was prepared by Buck and Ide's general method (*loc. cit.*). Methyl iodide (24 g.) was added to the dihydrobase (10 g.), dissolved in benzene (40 c.c.), and the mixture set aside at room temperature for 30 minutes. The yellow solid was collected, pressed nearly dry, and crystallized from alcohol; it formed fine, yellow needles (15·6 g., 90%), m. p. 201—202°. Späth and Epstein (*loc. cit.*) reported m. p. 202°.

6 : 7-*Methylenedioxy*-4-*nitro*-3-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-isoquinolyl)-*phthalide* [*Nitro*-(±)-*corlumine*] (I; R = NO_2).—Lodal (2·9 g.) and 6 : 7-methylenedioxy-4-nitrophthalide (1 g.) were refluxed in alcohol (100 c.c.) for 20 minutes and afforded orange, rectangular crystals (1·63 g., 85% of recrystallized product), m. p. 180—181° (decomp.) (Found: C, 58·9; H, 4·8; N, 6·7. Calc. for $C_{21}H_{20}O_8N_2$: C, 58·9; H, 4·7; N, 6·5%). The observed m. p. agrees with that recorded by Groenewoud and Robinson (*loc. cit.*). The base is phototropic and is easily cleaved by alcoholic hydrogen chloride.

Amino-(±)- *corlumine* (I; R = NH_2).—Several unsuccessful attempts were made to reduce nitro-(±)-corlumine, various solvents and catalysts being used. The following procedure was finally adopted. Nitro-(±)-corlumine (0·5 g.), dry benzene (150 c.c.), and Raney nickel were shaken with hydrogen at 500 lbs./sq. in. in a steel bomb (300 c.c.) at 50—60° for 1 hour. The bomb contents were filtered, and the bomb and the Raney-nickel sludge thoroughly washed with hot, dry benzene. The benzene was removed by distillation at reduced pressure under dry nitrogen. The amine crystallised from chloroform–methanol in clusters of short, pale-yellow needles (0·31 g., 66%), m. p. 221—223° (decomp.) (Found: C, 63·1; H, 5·5; N, 7·1. Calc. for $C_{21}H_{22}O_6N_2$: C, 63·3; H, 5·6; N, 7·0%). Groenewoud and Robinson (*loc. cit.*) recorded m. p. 218—219°.

Benzamido-(±)-*corlumine Hydrochloride* (as I; R = NHBz).—Prepared from amino-(±)-corlumine and benzoyl chloride in benzene and recrystallized from alcohol, *benzamido*-(±)-*corlumine hydrochloride* was obtained in short, white needles, m. p. 204—205° (decomp.) (Found: C, 62·3; H, 5·1; N, 5·3. $C_{28}H_{26}O_7N_2$,HCl requires C, 62·4; H, 5·1; N, 5·2%).

Iodo-(±)-*corlumine* (I; R = I).—The amino-compound was converted into iodo-(±)-corlumine by the method employed by Groenewoud and Robinson (*loc. cit.*) for converting amino- into iodo-*x*-bicuculline. The yellow iodo-base was extremely phototropic and was consequently employed, after being washed with cold water and cold alcohol, directly for reduction to (±)-corlumine.

(±)-*Corlumine* (I; R = H)—(a) *By reduction of iodo*-(±)-*corlumine*. The iodo-base obtained above was shaken in a steel bomb (300 c.c. capacity) with alcohol (125 c.c.), Raney nickel (one-half teaspoon), and hydrogen at 500 lbs./sq. in. at 50—60° for 2 hours. The mixture was filtered, the nickel residue extracted with hot alcohol, and the united filtrates made basic by addition of ammonia solution and concentrated. The concentrate was diluted with water (50 c.c.), aqueous sodium hydroxide (1 c.c.; 3N) added, and the basic solution thoroughly extracted with chloroform. The dried extracts were concentrated, methanol added (charcoal), and the whole concentrated. (±)-*Corlumine* [0·26 g., 27%; based on 1 g. of amino-(±)-corlumine] crystallized in short, stout prisms, m. p. 193·5—195° (decomp.) (Found: C, 65·7; H, 5·6; N, 3·7. $C_{21}H_{21}O_6N$ requires C, 65·8; H, 5·5; N, 3·7%).

(b) *By deamination of amino*-(±)-*corlumine*. Aqueous sodium nitrite (0·3 g. in 4 c.c. of water) was slowly added to a solution of amino-(±)-corlumine (1 g.) in dilute hydrochloric acid (5 c.c. of water and 3 c.c. of hydrochloric acid, *d* 1·18) at 0° during 30 minutes; this was followed by the addition of 50% hypophosphorous acid (5 c.c.) during 1 hour. The mixture was stirred for another hour, and after being kept at 0° for 24 hours, was poured into water (100 c.c.), made basic by addition of ammonia solution, and the free base (0·26 g., 27%) isolated as described above. The base obtained by deamination of amino-(±)-corlumine was identical in all respects with that obtained by catalytic reduction of iodo-(±)-corlumine. In admixture with a

sample of natural (±)-adlumine, m. p. 190° (Manske, *Canadian J. Res.*, 1938, **16,** *B*, 89), the m. p. of our product was depressed 30°.

Resolution of (±)-*Corlumine.*—Methanolic solutions of (±)-corlumine (0·2 g. in 3 c.c.) and (+)-tartaric acid (0·08 g. in 4 c.c.) were mixed and heated to boiling; lustrous, white plates, m. p. 208—208·5° (decomp.) (with perceptible softening at 203°) of (−)-corlumine (+)-(hydrogen tartrate) then separated. The methanolic mother-liquors were treated with ether which precipitated the ill-defined (+)-corlumine (+)-(hydrogen tartrate); this began to swell at 110° and slowly fused to a viscous mass at 127—140°. (+)-Corlumine (+)-(hydrogen tartrate), prepared from naturally occurring (+)-corlumine (from Eastman Kodak Co., Rochester, N.Y.), exhibited the same ill-defined behaviour as the corresponding salt from synthetic (±)-corlumine.

The individual hydrogen tartrates, obtained from the resolution of (±)-corlumine, were decomposed by ammonia solution, and the free bases extracted with chloroform. The properties of the enantiomorphs and natural (+)-corlumine are listed in the Table.

	$[\alpha]_D^{26}$	M. p.
(−)-Corlumine (synthetic)	−73·0° (*c*, 1·32 in $CHCl_3$)	158—160° (decomp.)
(+)-Corlumine (synthetic)	+75·0° (*c*, 1·18 in $CHCl_3$)	154—158·5 (decomp.)
(+)-Corlumine (natural)	+77·3° (*c*, 1·13 in $CHCl_3$)	158—160 (decomp.)

In admixture, synthetic and natural (+)-corlumine had m. p. 156—159° (decomp.). To (+)-corlumine, its optical antipode as yet not having been found in Nature, Manske (*Canadian J. Res.*, 1936, **16**, *B*, 349) attributed m. p. 159° and $[\alpha]_D^{25}$ +77° (*c*, 0·8 in $CHCl_3$).

The racemic modification of corlumine was prepared by dissolving equal amounts of natural (+)-corlumine and synthetic (−)-corlumine in chloroform and concentrating the solution to a small volume. Methanol was then added and the remainder of the chloroform evaporated. When the solution cooled, short, stout prisms, m. p. 193·5—194·5° (decomp.), of (±)-corlumine separated. In admixture with completely synthetic (±)-corlumine, the m. p. of the half natural, half synthetic product was not depressed.

The authors are indebted to Dr. R. H. F. Manske, who generously supplied a sample of (±)-adlumine.

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218. *The Reaction of* 1 : 4-*Diphenyl- and* 1 : 1 : 4-*Triphenyl-butane with* N-*Bromosuccinimide.*

By Shalom Israelashvili and Felix Bergmann.

Just as 1 : 2-diphenylethane is dehydrogenated to stilbene by *N*-bromosuccinimide, so 1 : 4-diphenylbutane is converted into 1 : 4-diphenylbutadiene *via* a crystalline dibromide. Under the same conditions 1 : 1 : 4-triphenylbutane gives a monobromo-1 : 1 : 4-triphenylbutadiene, containing bromine in the chain. An isomeric monobromo-derivative is obtained by interaction of 1 : 1 : 4-triphenylbutadiene with elementary bromine. The mechanism of these reactions is discussed.

N-Bromosuccinimide has been shown to replace an α-hydrogen atom in the benzyl group by bromine (Schmid and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573). In suitable cases this reaction can be used for dehydrogenation of saturated aliphatic bonds, Barnes (*J. Amer. Chem. Soc.*, 1948, **70**, 145) having converted 1 : 2-diphenylethane into stilbene. When we treated 1 : 4-diphenylbutane with *N*-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide, we obtained a crystalline dibromide, to which formula (I) is ascribed, since upon being refluxed with pyridine (Ruzicka, Plattner, and

Heusser, *Helv. Chim. Acta*, 1946, **29**, 473) it loses two moles of hydrogen bromide to give 1 : 4-diphenylbutadiene in good yield :

$$Ph\cdot[CH_2]_4\cdot Ph \xrightarrow[76\%]{+\ 2\ \text{Bromosuccinimide}} Ph\cdot CHBr\cdot CH_2\cdot CH_2\cdot CHBr\cdot Ph \xrightarrow[57\%]{\text{Pyridine}} Ph\cdot CH{:}CH\cdot CH{:}CH\cdot Ph$$

(I)

The yield of succinimide in the first step is quantitative, and the dibromide was isolated in 76% yield.

Application of this method to 1 : 1 : 4-triphenylbutane led to direct evolution of hydrogen bromide. After removal of the succinimide a viscous oil remained, which upon dehydrobromination with potassium acetate yielded a monobromo-1 : 1 : 4-triphenylbutadiene, m. p. 128° (III*a* or *b*). The probable explanation of this result is that a diphenylmethyl group reacts faster with *N*-bromosuccinimide than does a benzyl group (Buu-Hoï, *Annalen*, 1944, **556**, 1). The tertiary bromide thus formed easily loses hydrogen bromide to give a butene, which now contains two active sites for attack : one allylic and one benzylic position. Thus the dibromide (II) can be formed, which is converted by acetate into a monobromo-derivative. The course of the reaction can be depicted as follows :

$$CHPh_2\cdot[CH_2]_3\cdot Ph \xrightarrow{+\ \text{Bromo-succinimide}} CBrPh_2\cdot[CH_2]_3\cdot Ph \xrightarrow[(\text{spontaneous})]{-\ HBr} CPh_2{:}CH\cdot[CH_2]_2\cdot Ph \xrightarrow{+\ 2\ \text{Bromo-succinimide}}$$

$$CPh_2{:}CH\cdot CHBr\cdot CHBr\cdot Ph \xrightarrow{KOAc} CPh_2{:}CH\cdot CBr{:}CH\cdot Ph \text{ or } \overset{1}{C}Ph_2{:}\overset{2}{C}H\cdot\overset{3}{C}H{:}\overset{4}{C}Br\cdot Ph$$

(II) (III*a*) (m. p. 128°) (III*b*)

When, however, 1 : 1 : 4-triphenylbutadiene was treated with bromine in carbon tetrachloride, a different monobromo-derivative, m. p. 151°, was obtained. In view of the fact that the double bond $C_{(3)}$–$C_{(4)}$ in triphenylbutadiene is more reactive towards bromine than is $C_{(1)}$–$C_{(2)}$ (see III*b*), it appears probable that the primary product is again a dibromide of structure (II). It can thus be assumed that the two monobromo-derivatives are geometrical isomers (although positional isomerism as in III*a* and III*b* cannot be excluded). The spectra of the two bromination products (see Table) show a close similarity to each other and to that of 1 : 1 : 4-triphenylbutadiene.

Absorption spectra of 1 : 1 : 4-*triphenylbutadiene and its isomeric monobromo-derivatives* (*in* 95% *alcohol*).

	Min.,		Max.,		Min.,		Max.,	
	λ (Å)	log ε	λ (Å)	log ε	λ (Å)	log ε	λ (Å)	log ε
1 : 1 : 4-Triphenylbutadiene	2200	4·1	2410	4·2	2680	3·7	3360	4·6
Monobromo-derivative, m. p. 151°	2190	4·0	2420	4·2	2720	3·7	3330	4·5
Monobromo-derivative, m. p. 128°	2210	4·1	2410	4·2	2720	3·7	3340	4·5

Oxidation of both monobromides with permanganate in acetone gave benzophenone, thus excluding the possibility of nuclear bromination in one of the *gem*-phenyl rings. It therefore seems probable that the third ring also remained unsubstituted and that elementary bromine, like *N*-bromosuccinimide, effects substitution in the chain.

1 : 1 : 4-Triphenylbutadiene was synthesized from phenylacetic acid and ββ-diphenylacraldehyde as described by F. Bergmann, Israelashvili, and Gottlieb (*J.*, 1952, 2522). When the aldehyde was condensed with benzylmagnesium chloride, the desired hydro-

$$CPh_2{:}CH\cdot CH{:}CHPh \xleftarrow{1:2\ \text{Addtn.}} CPh_2{:}CH\cdot CHO \xrightarrow{1:4\ \text{Addtn.}} CPh_2(CHPh)\cdot CH_2\cdot CHO\ (IV)$$

carbon could be isolated only in 7·5% yield, the main product (28%) being a saturated aldehyde (IV), as shown by comparison of its absorption spectrum with that of ββ-diphenylacraldehyde and by formation of characteristic carbonyl derivatives.

Experimental

Bromination of 1 : 4-*Diphenylbutane.*—A mixture of 1 : 4-diphenylbutane (2·1 g.), *N*-bromosuccinimide (3·6 g.), and benzoyl peroxide (50 mg.) in carbon tetrachloride (50 c.c.) was refluxed

for 30 minutes. The precipitated succinimide (2 g.) was filtered off, and the filtrate evaporated to dryness. The residue solidified upon trituration with ethanol. Recrystallization from this solvent gave the *dibromide* (I) (2·8 g.) as needles, m. p. 119° (Found : C, 52·5; H, 4·2. $C_{16}H_{16}Br_2$ requires C, 52·2; H, 4·3%).

A solution of this dibromide (1·2 g.) in pyridine (15 c.c.) was refluxed for 45 minutes. The solvent was removed *in vacuo*, and the residue steam-distilled. Plates appeared in the distillate, and after crystallization from alcohol these had m p. 151°, not depressed by admixture of an authentic sample of 1 : 4-diphenylbutadiene; the yield was 400 mg. (57%).

Reaction between ββ-Diphenylacraldehyde and Benzylmagnesium Chloride.—To a Grignard solution [from benzyl chloride (7 g.) and magnesium (1·5 g.) in dry ether] was added dropwise (1 hour) at 0° an ethereal solution of ββ-diphenylacraldehyde (10·8 g.). After being refluxed for 2 hours, the mixture was decomposed with ammonium chloride. The oily organic residue slowly deposited crystals (1 g.). After two crystallizations from butanol *ββγ-triphenylbutaldehyde* (IV) was obtained in colourless prisms, m. p. 157—159°, stable towards boiling 20% sulphuric acid (Found : C, 88·0; H, 6·6. $C_{22}H_{20}O$ requires C, 88·0; H, 6·7%); the *semicarbazone* crystallized from toluene–ligroin in long needles, m. p. 138° (Found : C, 77·1; H, 6·4; N, 11·6. $C_{23}H_{23}ON_3$ requires C, 77·3; H, 6·4; N, 11·8%), and the 2 : 4-*dinitrophenylhydrazone* from butanol in yellow prisms, m. p. 187—188° (Found : N, 12·3. $C_{28}H_{24}O_4N_4$ requires N, 11·7%).

The yellow oil, remaining after separation of the aldehyde, was fractionated *in vacuo*. The fraction of b. p. 210°/3 mm. (2 g.) was triturated with ethanol, and the solid so obtained was recrystallized from the same solvent. 1 : 1 : 4-Triphenylbutadiene formed needles, m. p. 101°, identical with the hydrocarbon described previously (Staudinger, *Ber.*, 1909, **42**, 4258; F. Bergmann, Israelashvili, and Gottlieb, *loc. cit.*).

Reactions of 1 : 1 : 4-*Triphenylbutadiene.*—*With bromine.* A solution of triphenylbutadiene (0·25 g.) in carbon tetrachloride (10 c.c.) was treated at 0° with a solution of bromine (400 mg.) in the same solvent and left in the dark for 24 hours. Copious evolution of hydrogen bromide occurred. The residue was triturated with methanol and recrystallized from light petroleum. The *monobromide* (III*a* or *b*) formed prisms, m. p. 151° (230 mg.) (Found : C, 73·5; H, 4·5; Br, 21·8. $C_{22}H_{17}Br$ requires C, 73·1; H, 4·7; Br, 22·2%).

With maleic anhydride. A mixture of triphenylbutadiene (1 g.) and maleic anhydride (4 g.) was heated at 180° during 2 hours, ethanol added, and the mixture left overnight. The *adduct* (1·2 g.), recrystallized from butyl acetate–acetic acid, had m. p. 171° (Found : C, 77·0; H, 5·2. $C_{26}H_{22}O_4,\frac{1}{2}H_2O$ requires C, 76·7; H, 5·6%).

Bromination of 1 : 1 : 4-*Triphenylbutane.*—A mixture of 1 : 1 : 4-triphenylbutane (1·3 g.), *N*-bromosuccinimde (1·6 g.), benzoyl peroxide (40 mg.), and carbon tetrachloride (25 c.c.) was refluxed for 30 minutes, hydrogen bromide being eliminated especially towards the end of the time. The precipitated succinimide (0·87 g.) was filtered off, the solvent evaporated, and the residual, viscous, yellow-brown oil (1·6 g.) dissolved in benzene (15 c.c.). Potassium acetate (7 g.) and glacial acetic acid (12 c.c.) were added, and the mixture was refluxed for 30 minutes. The solution was then poured into ice-cold sodium hydroxide solution, and the product extracted with ether. The ether residue crystallized upon treatment with cold ethanol. Recrystallization from the same solvent gave the *monobromide* (III*a* or *b*) as light yellow rods, m. p. 128° (Found : C, 73·2; H, 4·5. $C_{22}H_{17}Br$ requires C, 73·1; H, 4·7%).

Oxidation of Monobromides.—(i) The monobromide of m. p. 151° (1 g.) was treated with a solution of potassium permanganate (3 g.) in acetone (100 c.c.) at room temperature for 36 hours. The mixture was worked up in the usual way and gave as neutral reaction product benzophenone (100 mg.), identified as its 2 : 4-dinitrophenylhydrazone, m. p. 238°, by comparison with an authentic sample. (ii) Oxidation of the monobromide of m. p. 128° similarly afforded benzophenone as the sole neutral reaction product.

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219. *Molecular-orbital Calculations on the Benzoate Ion.*

By Carl M. Moser.

Five molecular-orbital calculations on the benzoate ion have given quantitative estimates of the changes in the predictions of physical and chemical properties brought about by the different methods used in these calculations to allow for the presence of the hetero-atoms in the molecule. The calculations now reported give a measure of the dependence of the predictions of bond lengths and chemical reactivity on: (1) Wheland's assumption to determine the value for β carbon–oxygen, namely, that the exchange integral β is proportional to the overlap integral S; (2) the difference of the Coulomb integral α of the carbon atom next to the oxygen atom from the standard α due to an inductive effect on this carbon atom; (3) the inclusion of the overlap integral S in the calculations.

The differences in the predictions of bond lengths are not very large and all occur in the dimensions of the carboxyl group. The presence or absence of an inductive effect on the carbon atom next to the oxygen atom appears to have little influence on the bond lengths predicted. Considerable variation is observed in the predictions of chemical reactivity from these calculations.

This paper reports the results of calculations from which there have been obtained some quantitative estimates of the changes in the predictions of chemical and physical properties due to the various methods used in the simple molecular-orbital calculations to allow for the presence of a hetero-atom in a molecule.

The benzoate anion was selected although for some of the predictions of chemical reactivity, particularly for electrophilic substitution (which is generally carried out in acid solution), it would have been preferable to use the acid itself rather than the anion. The experimental data relevant to benzoic acid are not yet available, but from the carbon–oxygen distances in aliphatic acids (cf. Morrison and Robertson, *J.*, 1949, 987) the assumption that the acid possesses an axis of symmetry passing through the carboxyl group and the ring in the plane of the molecule would appear to be unjustified. It did not seem to be justifiable to incur the added complications that would be introduced into the computations in considering the Coulomb terms of the oxygen atoms in the molecule to be different.

The only reported work on molecular-orbital calculations on benzoic acid is that by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2080) on benzene derivatives with hetero-atom substituents. They recognised that the Coulomb integral of the hetero-atom would be different from the "standard" carbon Coulomb integral since the electron affinities of hetero-atoms are different from that of carbon. Also they considered that a small inductive effect would be transmitted to the carbon atoms adjacent to the hetero-atoms. Wheland and Pauling did not consider that the values that should be assigned to β carbon–oxygen might be different from the standard value. Variations in the resonance integrals, β_{C-Y} (where Y refers to the hetero-atom) are to be expected (Coulson, *Trans. Faraday Soc.*, 1946, **42**, 106): the importance of these variations in β is greater than has often been supposed (cf. Coulson and De Heer, *J.*, 1952, 483).

Finally, there is the question of the inclusion of the overlap integral, S, between adjacent atomic orbitals. Chirgwin and Coulson (*Proc. Roy. Soc.*, 1950, *A*, **201**, 196) have shown that the inclusion makes no difference in the results of the calculations of the ground state of alternant hydrocarbons, although considerable improvement results in the correlation of calculations and experimental results of the excited states (Mulliken and Rieke, *J. Amer. Chem. Soc.*, 1941, **63**, 1770). Coulson and De Heer (*loc. cit.*) have suggested that the qualitative conclusions regarding the ground state of molecules containing a hetero-atom should not be seriously affected by the inclusion of overlap, but such inclusion is probably essential even in a qualitative discussion of the excited states of molecules that contain a hetero-atom (Chirgwin and Coulson, *loc. cit.*).

Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900) included overlap in his calculations on the orienting influence of substituents in aromatic compounds; he explicitly considered variations in the Coulomb integrals brought about by the presence of the hetero-atom and

the inductive effect on the neighbouring carbon atoms and also included a variation in the value given to β_{C-H} different from the standard value, but the assumption that he used in deciding on a value for β_{C-H} may not entirely satisfactory (see below).

Five calculations are now discussed. The importance of three assumptions is considered: (1) Wheland's assumption used in order to decide on a value for β_{C-O}; (2) the necessity to consider an inductive effect on the carbon atom next to the oxygen atom; and (3) the inclusion of the overlap integrals. The calculations will be tested by agreement between their predictions of (1) bond lengths and (2) chemical reactivity and the respective experimental values (in so far as these are available).

The values chosen for the various parameters (α_{oxygen}, etc.) in these calculations may not be the best possible, and further work on the effect of the variation of the values assigned to these parameters will be reported later.

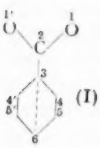
Wheland's Assumption.—In order to decide on a value for β_{C-Y}, Wheland (*loc. cit.*) assumed that the resonance integral for this bond is proportional to its overlap integral. He defined the symbol

$$\rho_{C-Y} = \beta_{C-Y}/\beta_X = S_{C-Y}/S_X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where S_{ij} has the usual meaning $\int \phi_i \phi_j d\tau$ (i and j are neighbouring atoms) and S_x refers to the "standard" overlap integral. Since the procedure for determining S_{ij} is straightforward (Mulliken, Rieke, Orloff, and Orloff, *J. Chem. Physics*, 1949, **17**, 2148), the use of Wheland's assumption implies that the value assigned to β_{C-H} can be readily determined.

In the application of this assumption to the present problem certain difficulties arise. Using the recipe of Mulliken *et al.* to determine S_{C-O} (the value of 1·23 Å was used as the length of the carbon–oxygen bond), one finds that $\rho_{C-O} = 0{\cdot}214/0{\cdot}250 = 0{\cdot}856$. Using Wheland's assumption one arrives at the conclusion that the value to be assigned to β_{C-O} is *less than* the value of β_X. However, previous workers have usually assumed that β_{C-O} is *greater than* β_X (Coulson, *Trans. Faraday Soc.*, 1946, **42**, 106; Dewar, *Nature*, 1950, **166**, 790; Brown, *J.*, 1951, 2670). The values assigned have been based on rather crude thermochemical considerations and are to be regarded as tentative. However, it seems probable that these values are of the right order of magnitude and there is certainly the possibility that Wheland's assumption should be modified so that the ratio of the β's is greater than the ratio of the S's.

In a detailed treatment of the self-consistent field molecular-orbital approximation, Mulliken (*J. Chim. physique*, 1949, **46**, 497, 675) has indicated that for carbon–carbon bonds β/S is approximately constant but that this would not be true for hetero-bonds. The further approximation that Wheland's assumption may not be justified involves no added difficulty in the computations. This can be illustrated by writing the benzoic acid anion as in (I) and considering the secular equation that arises from the wave functions that are symmetrical about the axis of symmetry. Using Wheland's notation as far as possible and remembering that $\gamma_X = \beta_X - S\alpha_X$, we have



(I)

$$\begin{vmatrix} \alpha_X + \delta_1\gamma_X - E & \rho_{12}(\beta_X - S_XE) + k\gamma_X & . & . & . & . \\ 2[\rho_{12}(\beta_X - S_XE) + k\gamma_X] & \alpha_X + \delta_2\gamma_X - E & \rho_{23}(\beta_X - S_XE) & . & . & . \\ . & \rho_{23}(\beta_X - S_XE) & \alpha - E & 2(\beta_X - S_XE) & . & . \\ . & . & \beta_X - S_XE & \alpha - E & \beta_X - S_XE & . \\ . & . & . & \beta_X - S_XE & \alpha - E & \beta_X - S_XE \\ . & . & . & . & 2(\beta_X - S_XE) & \alpha - E \end{vmatrix} = 0 \quad (2)$$

In (2) note has been made that the bond 2–3 is not a "standard" carbon–carbon bond; however, as mentioned above, Wheland's assumption does appear to be justified for such bonds. Equation (2) can readily be transformed into the more useful form (3), where $x = (\alpha - E)/(\beta_X - S_XE)$ and $\mathfrak{L} = 1 - S_X\delta$. Equation (4) becomes Wheland's assumption when $k = 0$.

$$\begin{vmatrix} \mathfrak{L}_1 x + \delta_1 & \rho_{12} + k(1 - S_0 x) & . & . & . & . \\ 2[\rho_{12} + k(1 - S_0 x)] & \mathfrak{L}_2 x + \delta_2 & \rho_{23} & . & . & . \\ . & \rho_{23} & x & 2 & . & . \\ . & . & 1 & x & 1 & . \\ . & . & . & 1 & x & 1 \\ . & . & . & . & 2 & x \end{vmatrix} = 0 \quad (3)$$

Calculations.—A solution for (3) requires a decision on values for δ_1, δ_2, and k. Wheland and Pauling chose the values $\delta_1 = 4$, $\delta_2 = 0{\cdot}8$; the former is twice as large as that used for α_{oxygen} by Brown (*J.*, 1951, 2670). The values $\delta_1 = 2$, $\delta_2 = 0{\cdot}4$ (for both β and γ) will be used in this paper. The value of $k = 0{\cdot}5$ was chosen in order to make the value of β_{C-O} approximately equal to $\sqrt{2}\,\beta_X$ if the overlap integral is neglected (cf. Brown, *loc. cit.*).

In the calculation of p_{12}, the choice of structure (C^+, O^- or C, O) for the carbon–oxygen bond makes a formal difference in the calculation of S. However, the numerical difference on calculation from either structure (presumably both make a contribution to the structure of the carbon–oxygen bond) is negligible. The calculation of p_{23} was made with the assumption that the $C_{(2)}$–$C_{(3)}$ bond distance is 1·5 Å.

The five calculations now reported are: (I) $\delta_1 = 2$, $\delta_2 = 0{\cdot}5$, $k = 0$ (Wheland's assumption); (II) $\delta_1 = 2$, $\delta_2 = 0{\cdot}4$, $k = 0{\cdot}5$; (III) $\delta_1 = 2$, $\delta_2 = 0$, $k = 0{\cdot}5$ (to assess the importance of the inductive effect $C_{(2)}$); (IV), $\alpha_O = \alpha_X + 2\beta$, $\alpha_{C(2)} = \alpha_X + 0{\cdot}4\ \beta$, $\beta_{C-O} = \sqrt{2}\beta$; (V) $\alpha_{C(2)} = \alpha_X$. In (IV) and (V) $\beta_{2\text{-}3} = \beta_X$. Calculations (IV) and (V) were carried out with neglect of the overlap integral.

The energies of the molecular orbitals for the calculations are listed in Table 1. The energies for calculations (I), (II), and (III) are given in the form $E = E_X + m\gamma_X$ where E_X is the energy of an electron in a $2p_z$ orbital in the standard alternant hydrocarbon γ_X has its usual meaning, and m is the numerical coefficient found from the secular equation. For calculations (IV) and (V) the form is $E = E_X + k\beta_X$; here k is the numerical coefficient found from the secular equation.

TABLE 1. *Energies of molecular orbitals of benzoic acid anion.*

Calc. :	(I)	(II)	(III)	(IV)	(V)
Symmetry	m (γ)	m (γ)	m (γ)	k (β)	k (β)
S	−4·32278	−4·40318	−4·47274	−2·14569	−2·20127
S	−1·79014	−2·06927	−2·26566	−1·43118	−1·54691
A	−1·33	−1·33	−1·33	−1·0	−1·0
S	−0·21802	−0·71517	−0·84729	−0·56208	−0·66043
A	0·8	0·8	0·8	1·0	1·0
S	0·88678	0·84064	0·83581	1·06775	1·06298
S	1·35261	1·34135	1·34066	2·0	2·0
A	2·0	2·0	2·0	2·0	2·0
S	2·17817	2·59395	2·53173	3·47120	3·34560

Charge density (q_μ) and mobile bonds orders ($p_{\mu\nu}$) can be computed from the formulæ given by Chirgwin and Coulson, but it is possible to recast these formulæ into slightly different but more convenient form. The formulæ (4) and (5) were suggested by R. D. Brown.

$$q_\mu = \sum_{j,\nu} n_j X_{j\mu} X_{j\nu} S_{\mu\nu} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$p_{\mu,\nu} = \tfrac{1}{2}\sum_{j,\rho} n_j (X_{j\mu} X_{j\rho} S_{\nu\rho} + X_{j\nu} X_{j\rho} S_{\mu\rho}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $S_{\mu\nu}$ is the overlap integral between atoms μ and ν, and $X_j\mu$, etc., are the coefficients of atom μ in orbital j, the occupied orbitals. In these equations n_j is the number of electrons in the jth orbital. Free valencies (F_μ) were computed from the formula (Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553)

$$F_\mu = 1{\cdot}414 - \Sigma p_{\mu\nu} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Localization energies, A, were calculated according to Wheland's method.

Bond Lengths.—Mobile bond orders (p) for the carbon–carbon bonds were converted into bond lengths (x, in Å) (Table 2) by the formula (Coulson, *Proc. Roy. Soc.*, 1939, *A*, **169**, 413) $x = s - (s - d)/[1 + K\,(1 - p)/p]$, where s and d are, respectively, the single- and double-bond distances, taken as 1·540 and 1·340 Å; K is a constant chosen so that the bond order–bond length curve passes through the triple-bond point (1·204 Å). With this condition $K = 0{\cdot}8095$. The length of the carbon–oxygen bond (bond 1–2) was obtained from the standard values of 1·43 and 1·215 Å for the carbon–oxygen single and double

bonds, respectively, suggested by Wirtz (*Z. Naturforsch.*, 1947, **2***a*, 264), and the value of the bond order in Å determined from a graph of these standard values against the appropriate bond order, namely, 0 and 0·652, 0·815, 0·823, 0·870, and 0·816 respectively for calculations (I), (II), (III), (IV), and (V). These bond orders are those obtained for a hypothetical C=O molecule under the assumptions of the various calculations. A curve approximating to that for the carbon–carbon bond was drawn between the standard points.

TABLE 2. *Bond orders* (p) *and bond lengths* (in Å).

Calc.:	(I)		(II)		(III)		(IV)		(V)	
Bond	*p*	Å	*p*	Å	*p*	Å	*p*	Å	*p*	Å
1—2	0·485	1·245	0·644	1·237	0·620	1·243	0·602	1·248	0·587	1·245
2—3	0·448	1·440	0·330	1·464	0·323	1·465	0·362	1·458	0·340	1·462
3—4	0·593	1·411	0·639	1·403	0·623	1·406	0·618	1·407	0·625	1·406
4—5	0·688	1·394	0·681	1·395	0·659	1·400	0·677	1·395	0·676	1·395
5—6	0·654	1·400	0·668	1·398	0·706	1·391	0·660	1·400	0·661	1·400

The numerous difficulties associated with the prediction of the lengths of carbon–hetero-atom bonds (see Coulson, *Proc. Roy. Soc.*, 1951, *A*, **207**, 63; *J. Phys. Chem.*, 1952, **56**, 311) suggest that the error in the predictions of these bond lengths may be considerable, certainly more than the usual uncertainty of about 0·02 Å associated with the prediction of bond lengths in alternant hydrocarbons by the simple M.O. procedure (Coulson, Daudel, and Robertson, *Proc. Roy. Soc.*, 1951, *A*, **207**, 306). Even if the standard values suggested by Wirtz are correct, the precise nature of the curve that should connect these points is unknown. The bond lengths assigned to the bond order of the carbon–oxygen bonds are only tentatively suggested, and may well need revision later.

The bonds of the benzene ring (bonds 3–4, 4–5, 5–6) are predicted to be nearly equal in length and all are within about 0·01 Å of the benzene bond length. No appreciable change in the bond distance of the ring appears to have been produced by the presence of the carboxyl group.

$C_{(2)}$–$C_{(3)}$ appears to possess considerable double-bond character, for the predicted bond length is considerably shorter than the 1·54 Å usually assigned to the single-bond length. The value predicted by calculation (I) is 0·018—0·025 Å less than that obtained by the other calculations. The error associated with this prediction may be somewhat larger than usual for here the change in the hybridization of $C_{(2)}$ will cause a change in the bond length–bond order curve (Coulson, "The Atomic Radius of Carbon," Memorial Volume to Victor Henri, Maison Desoer, Liége, 1947—48, p. 15), which has not been explicitly considered here.

All calculations lead to similar values for the carbon–oxygen bond length: inclusion of overlap generally leads to somewhat lower values than if it is neglected, but the differences are probably well within the limit of error inherent in the calculation. The lengths predicted by all the calculations are somewhat shorter (*ca.* 0·015—0·023 Å) than may be found from experiment (Wirtz, *loc. cit.*, suggests that the bond length of the carbon–oxygen bond in the carboxylic acid anion is 1·26 Å), but this is not surprising. The bond lengths of the benzoic acid anion apparently have not been measured; they are being investigated by Mr. S. Block and Professor J. D. H. Donnay in the Crystallographic Laboratory at Johns Hopkins University and will be of interest for comparison with the present calculations.

It is noteworthy that the choice of the bond distance in calculating the value of the overlap integral does not precisely predetermine the value that will be predicted for the bond length. The $C_{(2)}$–$C_{(3)}$ was presumed to be about 1·5 Å in determining *S* for this bond and by all calculations is predicted to be 0·09—0·10 Å shorter.

The differences in the predicted bond lengths in all five calculations are not very large: they all lead to practically the same values for the ring bonds. The maximum difference in the predicted carbon–oxygen bond length is only 0·03 Å, which is probably within the limits of error inherent in the prediction. The close agreement in bond lengths from calculations (II) and (III) on the one hand and from (IV) and (V) on the other suggests

that the inclusion or neglect of an inductive effect on the carbon atom next to the oxygen atom is not of great importance. Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **192**, 16) have shown that for an alternant hydrocarbon $dp/d\alpha$ is zero (bond-atom polarizability). Presumably the coefficient for a non-alternant hydrocarbon would still be very small. The difference in the predictions due to the inclusion or neglect of overlap also appears, from these calculations, to be negligible. The most important factor in these calculations causing an appreciable change in the predictions is the value assigned to β_{C-O}. This was to be expected from the work of Coulson and De Heer (*loc. cit.*).

Chemical Reactivity.—The data on the calculation of charge density (q), free valence (F), and localization energy for nucleophilic (A_n), electrophilic (A_e), and radical (A_r) substitution reactions are collected in Table 3. Loebl, Stein, and Weiss (*J.*, 1951, 405) found that, on hydroxylation of benzoic acid by free radicals produced by *X*-rays, the hydroxybenzoic acids were formed in the ratio $o : m : p = 5 : 2 : 10$. Dakin and Herter (*J. Biol. Chem.*, 1907, **3**, 419) studied the action of hydrogen peroxide on ammonium benzoate and found that approximately equal amounts of *o*-, *m*-, and *p*-hydroxybenzoic acids were formed. Holleman (*Rec. Trav. chim.*, 1899, **18**, 267) found that nitration of benzoic acid at 30° gave *o*-, *m*-, and *p*-nitrobenzoic acid in the ratio 22 : 76·5 : 1·2. The only data available on the nucleophilic reactions of benzoic acid are not suitable for the present purpose. Barth and Schreder (*Monatsh.*, 1882, **3**, 799) found that fusion of benzoic acid with potassium hydroxide afforded a complete mixture containing about 15% of *p*-hydroxybenzoic acid, some *m*-acid, and only a trace of salicylic acid.

TABLE 3.

Position	q	F	A_e	A_r	A_n	Position	q	F	A_e	A_r	A_n
	Calculation (I)						Calculation (IV)				
4	1·013	0·133	1·881	1·609	1·334	4	0·946	0·119	2·575	2·410	2·244
5	1·102	0·072	1·864	1·864	1·864	5	1·002	0·077	2·656	2·656	2·656
6	0·920	0·107	1·970	1·680	1·389	6	0·955	0·095	2·634	2·466	2·298
	Calculation (II)						Calculation (V)				
4	1·057	0·094	1·871	1·743	1·614	4	0·951	0·114	2·606	2·466	2·325
5	1·102	0·064	1·856	1·856	1·856	5	1·002	0·077	2·648	2·648	2·648
6	0·965	0·077	1·851	1·721	1·591	6	0·961	0·092	2·625	2·484	2·343
	Calculation (III)										
4	0·996	0·132	1·869	1·762	1·655						
5	1·136	0·049	1·857	1·857	1·857						
6	1·024	0·002	1·856	1·748	1·640						

In calculation (I) the predictions from both the values of q and of A_e are in agreement that electrophilic substitution should be in the order $m > o > p$, which agrees qualitatively with the experimental results quoted above. For quantitative comparison with experimental results it is necessary to assign a value to γ_X as well as to assume that the localization energies can be used to determine relative rates of reaction at the various free positions of the nucleus. With the choice of $\gamma_X = -34$ kcal. (Dewar, *Trans. Faraday Soc.*, 1946, **42**, 767), and with the assumptions that $RT = 0{\cdot}6$ kcal. and that the relative yield of a particular isomer is directly proportional to its relative reaction rate, and in view of the fact that there are two free *ortho*- and *meta*-, but only one *para*-position available, the A_e values from calculation (I) indicate that the isomers should be formed in the proportions $o : m : p = 24 : 75 : 0{\cdot}3$, in very good agreement with Holleman's results (*loc. cit.*). This agreement is very likely fortuitous: amongst the numerous errors inherent in the calculation, at least two should be mentioned: (1) the value chosen for γ_X and (2) the fact that the calculation started initially from a consideration of the anion. As for (1), the value of −34 kcal. for γ_X is rather less than that usually chosen to make a suitable fit of calculations with the experimental data of spectra. However, it may well be that the γ_X (spectroscopic) and γ_X (chemical reaction) are not identical, or, more pertinent, that the γ_X (electrophilic reaction), γ_X (nucleophilic reaction), and γ_X (radical reaction) may all be different. Even small changes in γ_X would cause considerable changes in the quantitative predictions of chemical reactivity. The error in (2) is difficult to assess, but it is possibly appreciable.

The predictions of electrophilic substitution from calculations (II) and (III) are not consistent from a consideration of the values of q and A_r and do not seem to be in qualitative agreement with the available experimental data.

If the overlap integral is neglected [as in calculations (IV) and (V)], one finds an order for nucleophilic substitution that is in qualitative agreement with experiment from the q values if an inductive effect is considered on carbon atom 2 but not if this inductive effect is neglected. The values of A_r are in agreement that the order should be $o > p > m$, which is not observed in experiment.

As mentioned on p. 1077, experimental evidence indicates that free-radical substitution of benzoic acid occurs nearly equally well on all three available positions of the benzene nucleus. From calculation (I), the predictions are not consistent from a consideration of the F and A_r values; this inconsistency would be accommodated, following Brown, by the assumption of the " crossing " of the π-energy plots (Brown, *Quart. Reviews*, 1952, **6**, 63). The considerable difference of about $0{\cdot}26\ \gamma$ between A_r (*ortho-para*) suggests that, if these predictions are to be made to fit with the experimental data, a value of γ_X (radical) considerably less than -34 kcal. would have to be used. The calculations without overlap are in agreement with calculation (I) that the order of substitution by free radicals should be $o > p > m$ (in these calculations both the F and A_r values are consistent in their predictions) but here again one would have to assign a smaller value than -17 kcal. to β_X (radical) in order to obtain agreement with experiment. In calculations (II) and (III) the A_r values appear to predict substitution that is in qualitative agreement with experiment.

For nucleophilic substitution, the predictions of calculation (I) from the values of q seem to be in better agreement with available experimental evidence than from the values of A_n, though the reverse seems to be true from (II) and (III). Calculations without overlap do not appear to agree with experiment on either basis. Unfortunately the experimental data available do not provide even a good qualitative guide for this type of substitution.

It is of interest that whereas the various calculations made only slightly different predictions as to the bond lengths, yet their predictions of chemical reactivity varied considerably. It seems likely that the latter predictions will prove the more delicate test for deciding which of the calculations most closely agrees with experimental results. Judgment on this point must be reserved until there is some better basis for more quantitative interpretations of the predictions of chemical reactivity.

A few general conclusions can be drawn from these calculations. The first is that inclusion or neglect of an inductive effect on the carbon atom next to the oxygen atom makes no qualitative difference in the predictions of chemical reactivity if the predictions are made from a consideration of the localization energies, but there is a difference in the predictions if these are made from the values of q. Perhaps even more important, it can be seen that, at least in the calculations now reported, the inclusion or neglect of overlap makes a considerable difference in the predictions of chemical reactivity. Previously, good agreement has been obtained between these predictions and experimental results in hetero-molecules from localization energies calculated without overlap. The results of the present calculations lead one to wonder if this agreement would still occur if the overlap integrals had been included in the calculations.

The helpful suggestions and interest shown by Professor C. A. Coulson, F.R.S., are gratefully acknowledged. The work was considerably aided by the advice of the members of the Theoretical Physics Department at King's College and, in particular, the author is indebted to Dr. R. D. Brown.

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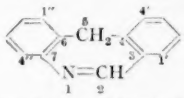
220. *Heterocyclic Derivatives of* 1 : 2-5 : 6-*Dibenzocyclohepta*-1 : 3 : 5-*triene. Part I.* 2 : 3-6 : 7-*Dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*trienes.*

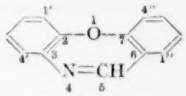
By C. I. Brodrick, (Miss) M. L. Donaldson, J. S. Nicholson, W. F. Short, and D. G. Wibberley.

Methods have been developed for the synthesis of the heterocyclic compounds indicated in the title. Examples of the fission of the seven-membered ring by methyl sulphate and by alcoholic sodium ethoxide are recorded.

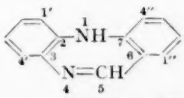
Note on Nomenclature.—The complex substances described in the memoirs comprising this series have, after consultation with the Editor, been named as illustrated for (I)—(IV).

(I) 

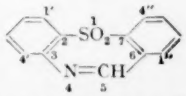
3 : 4-6 : 7-Dibenz-1-aza*cyclo*hepta-1 : 3 : 6-triene.

(II) 

2 : 3-6 : 7-Dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene

(III) 

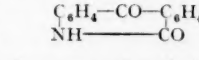
2 : 3-6 : 7-Dibenzo-1 : 4-diaza*cyclo*hepta-2 : 4 : 6-triene

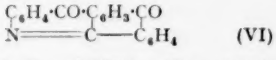
(IV) 

2 : 3-6 : 7-Dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene 1 : 1-dioxide

Intensification of the interest in homocyclic seven-membered rings owing to their presence in a number of natural products suggested the desirability of preparing heterocyclic analogues. For several reasons, including the therapeutic importance of various phenanthridine derivatives, it was decided in the first instance to prepare compounds containing ring systems in which an additional atom or group X (O, NR, S, SO_2, CH_2, etc.) was inserted between the benzene rings of phenanthridine. When X is an atom with a lone pair of electrons, the seven-membered ring might display quasi-aromatic properties since it would be relatively free from strain and may be derived by inserting the unsaturated unit ·CH:N· into a five-membered heterocyclic nucleus of the furan, thiophen, or pyrrole type (X = O, S, NR). The extent of the coherence of these units, with consequent production of an aromatic system, cannot be precisely foreseen, and is no doubt limited, *inter alia*, by the fact that it interferes with the independent conjugation of at least one of the benzene rings. The experimental results show that some of the systems exemplify the phenomenon of limited conjugation and the instability of the central ring then gives rise to some novel transformations.

An examination of the literature shows that the above heterocyclic systems are represented by only two compounds, both derived from (I). Beckmann and Liesche (*Ber.*, 1923, **56**, 17) showed that anthraquinone monoxime is converted by phosphorus pentachloride into 2 : 5-dioxo-3 : 4-6 : 7-dibenz-1-aza*cyclo*hepta-3 : 6-diene (V), which was

(V) 



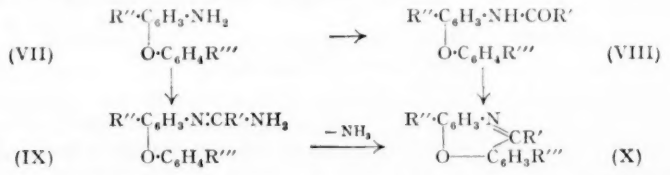
(VI)

designated 10-hydroxymorphanthrid-9-one by Scholl and Müller (*Ber.*, 1931, **64**, 640), who coined the name " morphanthridine " for (I), because this heterocyclic system is contained in Knorr's now obsolete formula for morphine. Scholl and Müller assigned the structure (VI) to the dehydration product of 1-benzoylanthraquinone 9-monoxime.

Three methods for the preparation of 2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-trienes (type II) have now been devised and the compounds prepared are enumerated in the Table.

Method I. The Bischler–Napieralski type of ring closure can be applied to 2-acylamino-

diphenyl ethers (VIII), phosphoryl chloride usually being employed as condensing agent but better results being obtained in one case (No. 6) by using phosphorus pentachloride.



Method II. The benzenesulphonate of a 2-aminodiphenyl ether (VII) was fused with a nitrile R'·CN giving the amidine (IX) (Oxley and Short, *J.*, 1946, **147**) which on being boiled with phosphoryl chloride and nitrobenzene afforded the cyclic compound (X). Similar syntheses of phenanthridines and of dihydro*iso*quinolines from amidines have already been described (Cymerman and Short, *J.*, 1949, **703**; Brodrick and Short, *J.*, 1951, 1343).

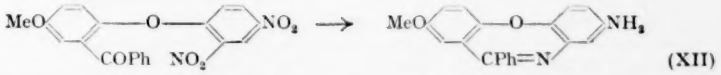
2 : 3-6 : 7-*Dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*trienes*.

No.	Substituents	Method	Yield, %	M. p.	Formula	Found, % C	H	N	Required, % C	H	N
(1)	5-*Phenyl*-	I	80	81°	$C_{19}H_{13}ON$	82·9	4·8	5·1	84·1	4·8	5·2
		II	78	,,		—	—	—	—	—	—
(2)	2''-*Bromo*-5-*phenyl*-	I	33	141—142	$C_{19}H_{12}ONBr$	65·5	3·5	4·1	65·1	3·4	4·0
			56	,,		—	—	—	—	—	—
(3)	3'-*Bromo*-5-*phenyl*-	I	37	120·5—121·5	$C_{19}H_{12}ONBr$	64·7	3·5	4·5	65·1	3·4	4·0
(4)	2''-*Methoxy*-5-*phenyl*-	I	54	138—139·5	$C_{20}H_{15}O_2N$	79·5	5·1	4·8	79·7	5·0	4·65
(5)	2'' : 3'-*Dibromo*-5-*phenyl*-	I	58	204—205	$C_{19}H_{11}ONBr_2$	53·2	2·4	3·4	53·15	2·6	3·3
			74	,,		—	—	—	—	—	—
(6)	2'' : 3'-*Dicyano*-5-*phenyl*-	I	60	265—267	$C_{21}H_{11}ON_3$	79·05	3·9	—	78·5	3·4	—
			23	,,		—	—	—	—	—	—
(7)	3'-*Amino*-2''-*methoxy*-5-*phenyl*-	III	47	141·5—143	$C_{20}H_{16}O_2N_2$	76·4	4·8	—	75·95	5·1	—
(8)	3'-*Nitro*-5-p-*nitrophenyl*-	I	55	264	$C_{19}H_{11}O_5N_3$	63·0	3·0	11·7	63·2	3·05	11·6
(9)	2''-*Methoxy*-5-p-*nitrophenyl*-	I	83	182—184	$C_{20}H_{14}O_4N_2$	69·5	3·95	8·4	69·4	4·0	8·1
(10)	2''-*Bromo*-5-p-*cyanophenyl*-	I	66	216—217	$C_{20}H_{11}ON_2Br$	—	—	7·6	—	—	7·5
(11)	3'-*Bromo*-5-p-*cyanophenyl*-	I	45	208—209	$C_{20}H_{11}ON_2Br$	—	—	7·8	—	—	7·5
(12)	5-p-*Cyanophenyl*-2''-*methoxy*-	I	85	180—182	$C_{21}H_{14}O_2N_2$	77·6	4·4	8·8	77·3	4·3	8·6
(13)	2''-*Methoxy*-5-p-*methylsulphonylphenyl*-	II	30	150—152	$C_{21}H_{17}O_4NS$	—	—	3·8	—	—	3·7
(14)	2''-*Methoxy*-5-2-*pyridyl*-	I	62	127—129·5	$C_{19}H_{14}O_2N_2$	75·8	4·7	9·6	75·5	4·65	9·3

(1) The *picrate* crystallised from alcohol in yellow needles, m. p. 149—150° (Found: N, 11·3, 11·4. $C_{25}H_{16}O_8N_4$ requires N, 11·2%). The *hydrochloride*, prepared in dry ether, had m. p. 135—136° (Found: N, 4·3. $C_{19}H_{14}ONCl$ requires N, 4·55%). (2) and (5) The higher yields were obtained by a modified procedure designated the " direct method " in the Experimental section. (6) The higher and lower yields were obtained with phosphorus pentachloride and phosphoryl chloride respectively. The dicyanide was also prepared from the corresponding dibromo-compound as described in the Experimental section. (7) The *picrate* crystallised from alcohol in clustered yellow needles, m. p. 175° (decomp.) after softening at 150° (Found: N, 12·7. $C_{26}H_{19}O_9N_5$ requires N, 12·8%). (9) The nitro-compound (1 g.), suspended in ethyl acetate (50 c.c.), was reduced for 15 hours under atmospheric conditions in presence of Raney nickel (0·6 g.), giving yellow prisms of 5-p-*aminophenyl*-2''-*methoxy*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (79%), m. p. 177—179° (Found: N, 9·0. $C_{20}H_{16}O_2N_2$ requires N, 8·9%).

The intermediate 2-aminodiphenyl ethers (VII) were obtained from the corresponding nitro-compounds which were usually prepared by the Ullmann method and only one point calls for comment. Bogert and Evans (*Ind. Eng. Chem.*, 1926, **18**, 300) state that reduction of 2 : 4-dinitrodiphenyl ether with stannous chloride affords 4-amino-2-nitrodiphenyl ether, whereas Brewster and Strain (*J. Amer. Chem. Soc.*, 1934, **56**, 117) regard the product as 2-amino-4-nitrodiphenyl ether. The synthesis of 3'-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene (No. 8) from this amine shows that the amino-group is in the 2-position.

Method III. This method is exemplified by the preparation of 3′-amino-2″-methoxy-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene (No. 7). 2-Hydroxy-5-methoxybenzophenone and 1-chloro-2 : 4-dinitrobenzene gave 2-(2 : 4-dinitrophenoxy)-5-methoxybenzophenone (XI), which afforded the cyclic compound (XII) on catalytic reduction in presence of Raney nickel.

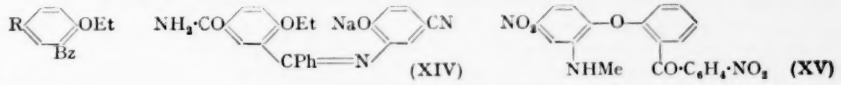


(XI) (XII)

The bromo-compounds numbered (5), (10), and (11) in the Table were converted into the corresponding dicyanides (by the action of cuprous cyanide in boiling quinoline), and the first two then into the diamidines by the Pinner method.

Attempts to reduce 2″ : 3′-dicyano-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene with sodium and ethanol resulted in the fission of the ether linkage by sodium ethoxide, the nature of the products obtained depending on the method of isolation adopted. When water was introduced into the cooled reaction mixture, 5-cyano-2-ethoxybenzophenone (XIII; R = CN) was obtained, but when water was added before removal of alcohol the products isolated were the sodium salt (XIV) of 5-carbamyl-2-ethoxybenzophenone 5-cyano-2-hydroxyphenylimine, 5-carbamyl-2-ethoxybenzophenone (XIII; R = $CO{\cdot}NH_2$), and 5-carboxy-2-ethoxybenzophenone (XIII; R = CO_2H). The structures of these compounds follow from their interrelation and the identity of the acid (XIII; R = CO_2H) with a specimen obtained by oxidising 2-ethoxy-5-methylbenzophenone (XIII; R = Me) (Auwers, *Ber.*, 1903, **36**, 3892) with potassium permanganate. The first step in the fission of the ether presumably involves attraction of the ethoxide ion to position 7 and, in view of the relatively small attraction of electrons by the cyano-group (cf. Hargreaves and McGookin, *J. Soc. Chem. Ind.*, 1950, **69**, 186), the electromeric effect of the nitrogen atom in position 4 probably plays a more important part than the cyano-group in position 2″ in withdrawing electrons from $C_{(7)}$.

Dr. A. E. S. Fairfull investigated the methylation of 3′-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene (No. 8) and found that fission of the heterocyclic nucleus readily occurs. The heterocyclic compound and methyl sulphate afford a gum, probably the methomethylsulphate, which gives orange-red prisms, m. p. 152—153°, on crystallisation from methanol, the change being facilitated by the addition of a little water. This compound behaves as an amino-ketone, giving a 2 : 4-dinitrophenylhydrazone and colourless, readily hydrolysed salts with mineral acids, and is formulated as 2-(2-methylamino-4-nitrophenoxy)-4′-nitrobenzophenone (XV), being produced by hydrolysis of the methomethylsulphate, followed by isomerisation of the methohydroxide successively to the alcohol and the amino-ketone : $\cdot CPh{:}\overset{+}{N}Me\cdot\}Me\bar{S}O_4 \longrightarrow HO\cdot\dot{C}Ph\cdot NHMe \longrightarrow$ (XV).



(XIII) (XIV) (XV)

Experimental

Preparation of intermediates.

2-*Benzamidodiphenyl Ether*.—2-Nitrodiphenyl ether (Brewster and Groening, *Org. Synth.*, 1934, **14**, 66) was reduced as described by Ullmann (*Ber.*, 1896, **29**, 1881) and the crude amine was benzoylated directly, giving 2-*benzamidodiphenyl ether* (61%), m. p. 76·5—77° (Found : C, 78·85; H, 5·6; N, 5·1. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2; N, 4·8%).

2-*Benzamido*-4′-*bromodiphenyl Ether*.—4′-Bromo-2-nitrodiphenyl ether (98 g.), prepared by Henley's method (*J.*, 1930, 1223), reduced iron powder (88 g.), water (98 c.c.), and hydrated ferric chloride (0·9 g.) were stirred and heated on the steam-bath for an hour, and the amine was collected in ether. The amine hydrochloride (75·5%), m. p. 183—185°, was precipitated by the addition of concentrated hydrochloric acid, and acetylation gave 2-acetamido-4′-bromodiphenyl ether, m. p. 105—106° in agreement with McCombie, Macmillan, and Scarborough (*J.*, 1930, 1206). Benzoylation in 10% aqueous sodium hydroxide at room temperature afforded 2-*benz*-

amido-4'-bromodiphenyl ether (53%), m. p. 98—99° (Found: N, 3·9. $C_{18}H_{14}O_2NBr$ requires N, 3·8%).

2-*Benzamido-4-bromodiphenyl Ether.*—4-Bromo-2-nitrodiphenyl ether, prepared in 85% yield by Henley's method (*loc. cit.*), gave 2-amino-4-bromodiphenyl ether (37%), m. p. 53—54°, when reduced with iron and aqueous ferric chloride as described above. McCombie, Macmillan, and Scarborough (*loc. cit.*) record m. p. 54°. The amine was benzoylated in nitrobenzene, and the solution of the benzamido-compound was treated with phosphoryl chloride (see below).

2-*Benzamido-4'-methoxydiphenyl Ether.*—2-Amino-4'-methoxydiphenyl ether hydrochloride (2·5 g.; Mole and Turner, *J.*, 1939, 1720), ether (10 c.c.), benzoyl chloride (1·5 g.), and N-sodium hydroxide (40 c.c.) were shaken for 5 minutes, and the resulting solid was recrystallised from alcohol, giving 2-*benzamido-4'-methoxydiphenyl ether* (88%), m. p. 135·5—136·5° (Found: N, 4·75. $C_{20}H_{17}O_3N$ requires N, 4·4%). 4-*Nitro*-2-p-*nitrobenzamidodiphenyl ether*, prepared from 2-amino-4-nitrodiphenyl ether (Bogert and Evans, *loc. cit.*), crystallised from alcohol in colourless needles, m. p. 173° (Found: N, 11·1. $C_{19}H_{13}O_6N_3$ requires N, 11·1%).

4'-*Methoxy*-2-p-*nitrobenzamidodiphenyl ether* (82%), prepared similarly to the benzamido-compound, separated from alcohol in yellow blades, m. p. 132—133° (Found: N, 7·8. $C_{20}H_{16}O_5N_2$ requires N, 7·7%). *p*-Cyanobenzoyl chloride (83%), m. p. 65—66°, was obtained by the method of Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 115), but the residue obtained by removing excess of thionyl chloride was crystallised directly from benzene–light petroleum (1 : 2). 2-p-*Cyanobenzamido-4'-methoxydiphenyl ether* (74%), prepared from this chloride, had m. p. 119—121° (Found: N, 8·0. $C_{21}H_{16}O_3N_2$ requires N, 8·1%). Nicotinoyl chloride hydrochloride, prepared from nicotinic acid (5·7 g.) and thionyl chloride (20 c.c.) (Späth and Spitzer, *Ber.*, 1926, **59**, 1477), slowly dissolved in boiling chlorobenzene (63 c.c.), and the resulting solution was boiled for 5 minutes with a solution of 2-amino-4'-methoxydiphenyl ether (10 g.) in warm chlorobenzene (16 c.c.). The product was extracted into 5N-hydrochloric acid, liberated by ammonia, and crystallised from a large volume of light petroleum, giving rods (43%) of 4'-*methoxy*-2-*nicotinamidodiphenyl ether*, m. p. 93—94° (Found: N, 8·9. $C_{19}H_{16}O_3N_2$ requires N, 8·75%).

2-*Benzamido-4* : 4'-*dibromodiphenyl Ether.*—The corresponding nitro-compound, prepared in 71% yield by Henley's method (*loc. cit.*), gave an 83% yield of 2-amino-4 : 4'-dibromodiphenyl ether hydrochloride, m. p. 176—177°, on reduction with iron and aqueous ferric chloride, the technique described above being used. The amine had m. p. 68—69° (McCombie, Macmillan, and Scarborough, *loc. cit.*, p. 1207, record m. p. 70°) and benzoylation in 10% aqueous sodium hydroxide gave 2-*benzamido-4* : 4'-*dibromodiphenyl ether*, m. p. 132—133° (Found: N, 3·2. $C_{19}H_{13}O_2NBr_2$ requires N, 3·1%).

2-*Benzamido-4* : 4'-*dicyanodiphenyl Ether.*—The corresponding amine (6·4 g.; Berg and Newbery, *J.*, 1949, 645), benzoyl chloride (10 g.), and pyridine (50 c.c.) were boiled for 30 minutes, and the product was isolated and recrystallised from ethyl acetate, giving prisms (73%) of 2-*benzamido-4* : 4'-*dicyanodiphenyl ether*, m. p. 177° (Found: N, 12·4. $C_{21}H_{13}O_2N_3$ requires N, 12·4%).

2-(2 : 4-*Dinitrophenoxy*)-5-*methoxybenzophenone.*—2-Hydroxy-5-methoxybenzophenone (5 g.; Bogert and Howells, *J. Amer. Chem. Soc.*, 1930, **52**, 840), 1-chloro-2 : 4-dinitrobenzene (4·5 g.), and alcoholic sodium ethoxide (from 0·51 g. of sodium and 25 c.c. of absolute alcohol) were boiled for an hour, then cooled, and the resulting solid washed successively with 95% alcohol, water, and 95% alcohol, leaving the crude product (61%). Crystallisation from alcohol gave colourless prisms of 2-(2 : 4-*dinitrophenoxy*)-5-*methoxybenzophenone*, m. p. 126·5—128·5° (Found: N, 7·1. $C_{20}H_{14}O_7N_2$ requires N, 7·1%).

2 : 3-6 : 7-*Dibenz*-1-*oxa*-4-*aza*cyclo-2 : 4 : 6-*trienes.*

Method I.—The mixture of amide (0·7—30 g.), phosphoryl chloride (1—1·4 c.c. per g. of amide) and nitrobenzene (0—4 c.c. per g. of amide) was heated in an oil-bath at 170—190°, or when no nitrobenzene was used (Nos. 4, 9, and 12) so that the mixture boiled gently. Evolution of hydrogen chloride was complete in 3—7 hours except in example 14 where the mixture was heated for 20 hours. Somewhat different proportions of reactants were used in the preparation of compound no. 6 and the method is described below in detail, together with the alternative method using phosphorus pentachloride and stannic chloride. Compound no. 3 was prepared by the direct method (described below) in which the aminodiphenyl ether was benzoylated and the amide treated directly with phosphoryl chloride, and this method was also used in alternative preparations of compounds nos. 2 and 5. The methods employed for the isolation of the oxa-aza-compounds are sufficiently illustrated by the detailed examples given below.

2″ : 3′-*Dicyano*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 6). (1) A low yield (23%) of this compound was obtained by heating 2-benzamido-4 : 4′-dicyanodiphenyl ether (0·7 g.), phosphoryl chloride (2 c.c., 10·5 mols.), and nitrobenzene (6 c.c.) at 180° for 6 hours. (2) Phosphorus pentachloride (0·9 g., 2·1 mols.) in hot nitrobenzene (10 c.c.) was added to a solution of 2-benzamido-4 : 4′-dicyanodiphenyl ether (0·7 g.) in nitrobenzene (20 c.c.) at 130°, the temperature was then raised to 210°, stannic chloride (2 drops) was added, and the mixture was boiled for 2 hours. The dark residue obtained when nitrobenzene had been removed at 100° under reduced pressure afforded the crude oxa-aza-compound (0·4 g., 60%), and recrystallisation from alcohol gave colourless plates of the pure compound, m. p. 265—267°, which gave the analytical results recorded in the Table. (3) 2″ : 3′-Dibromo-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-triene (no. 5) (4·4 g.) and cuprous cyanide (5·0 g., 5·4 mols.) were added during 15 minutes to boiling quinoline (20 c.c.) and, after the mixture had been boiled for another 30 minutes, it was cooled to 100° and poured into excess of 3N-hydrochloric acid. The solid was washed with dilute acid and recrystallised from 2-ethoxyethanol, giving the crude cyanide, m. p. 260—263° (1·15 g., 36%). Vacuum-sublimation and a further crystallisation raised the m. p. to 265—267°, undepressed on admixture with a specimen prepared by the first method (Found : C, 77·8; H, 3·5; N, 13·2. Calc. for $C_{21}H_{11}ON_3$: C, 78·5; H, 3·4; N, 13·1%). The use of less cuprous cyanide resulted in the survival of unchanged bromo-compound and the product was then very difficult to purify.

3′-*Bromo*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 3). A mixture of 2-amino-4-bromodiphenyl ether (6·6 g.), benzene (12·5 c.c.) and nitrobenzene (37·5 c.c.) was distilled until the internal temperature reached 210° and was then cooled to 185° and kept at this temperature during the slow (20 minutes) addition of benzoyl chloride (3·1 c.c., 1·1 mols.). The temperature was then kept at 212° for 15 minutes, and lowered to 205° before the addition of phosphoryl chloride (2·5 c.c., 1·2 mols.). After the mixture had been boiled for 2 hours, part of the solvent was removed by distillation (15 c.c.), and the residue was cooled, shaken with aqueous sodium hydroxide, and extracted with chloroform. The black brittle solid which remained when the solvents were removed at 100° under reduced pressure was crystallised from 2-ethoxyethanol and gave the crude cyclic compound, m. p. 120—122° (3·2 g., 37%). A sample recrystallised from the same solvent had m. p. 120·5—121·5° and gave the analytical results shown in the Table.

2″-*Bromo*- (*no.* 2) *and* 2″ : 3′-*dibromo*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 5) were similarly prepared in 56 and 74% yield respectively.

Method II.—5-*Phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 1). o-*Phenoxyphenylammonium benzenesulphonate*, obtained in 95% yield from the acid and amine in alcohol, separated from alcohol–ether in colourless crystals, m. p. 150—151° (Found : N, 4·4. $C_{18}H_{17}O_4NS$ requires N, 4·1%). When this salt (11·4 g.) and phenyl cyanide (3·4 g.) were heated at 200° for 2½ hours, N-o-*phenoxyphenylbenzamidine* was obtained in 72% yield and after crystallisation from benzene–light petroleum had m. p. 120—121° (Found : N, 10·1. $C_{19}H_{16}ON_2$ requires N, 9·7%). The amidine (2·4 g.), phosphoryl chloride (3·8 c.c., 5 mols.), and nitrobenzene (16 c.c.) were boiled under reflux for 4 hours, the temperature rising from 160° to 175°, and, after the nitrobenzene had been removed by distillation under reduced pressure, the mixture was cooled and triturated with 5N-sodium hydroxide. The oxa-aza-compound was collected in ether and converted into its *picrate* (2·7 g., 64%), which after crystallisation from alcohol had m. p. 150°, undepressed on admixture with a sample prepared by method I (Found : N, 11·4. $C_{25}H_{16}O_8N_4$ requires N, 11·2%).

2″-*Methoxy*-5-p-*methylsulphonylphenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 13). 2-Amino-4′-methoxydiphenyl ether benzenesulphonate (6·7 g.; m. p. 179—181°) and *p*-cyanophenyl methyl sulphone (3·3 g.) were heated at 210° for 2 hours, and then extracted with a large volume of boiling water. The aqueous solution was extracted with chloroform, then made alkaline, and the amidine collected in chloroform. Crystallisation from 95% alcohol afforded colourless needles (0·92 g., 13%) of N-(o-4-*methoxyphenoxyphenyl*)-p-*methylsulphonylbenzamidine*, m. p. 146—147° (Found : N, 7·2. $C_{21}H_{20}O_4N_2S$ requires N, 7·1%). When the amidine (0·7 g.) and phosphoryl chloride (2 c.c., 12·5 mols.) were boiled together for 5 hours, the oxa-aza-compound was obtained in 30% yield as a non-basic solid which crystallised from methanol in pale yellow needles, m. p. 150—152°, and gave the analytical results recorded in the Table.

Method III.—3′-*Amino*-2″-*methoxy*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (*no.* 7). 2-(2 : 4-Dinitrophenoxy)-5-methoxybenzophenone (0·8 g.) was dissolved in ethyl acetate (50 c.c.) and shaken with Raney nickel (1 g.) in hydrogen. Under atmospheric conditions

the reduction was complete in 16 hours, and the gum obtained after removal of the catalyst and the solvent was dissolved in 5N-hydrochloric acid (30 c.c.). The acid solution was extracted with ether, then made alkaline with ammonia, and the product collected in ether. Evaporation of the ethereal solution gave a gum which solidified on trituration with methanol, and crystallisation from the same solvent gave the oxa-aza-compound, m. p. 140—142° (0·3 g., 47%). Further crystallisation raised the m. p. to 141·5—143° and the sample gave the analytical results recorded in the Table.

Preparation of cyanides and amidines.

2''- *and* 3'-*Cyano*-5-p-*cyanophenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—These cyanides were obtained in 62 and 38% yield respectively when the 2''- and 3'-bromo-compounds (35 g.) and cuprous cyanide (18·5 g., 2·2 mols.) were added during 15 minutes to boiling quinoline (150 c.c.), the mixtures being boiled for a further 30 minutes and then poured into 2N-hydrochloric acid. The cyanides were purified by crystallisation from 2-ethoxyethanol. 2''-*Cyano*-5-p-*cyanophenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* had m. p. 243—244° (Found: C, 78·5; H, 3·4; N, 13·4%) and 3'-*cyano*-5-p-*cyanophenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* had m. p. 233—234° (Found: C, 77·8; H, 3·35; N, 13·3. $C_{21}H_{11}ON_3$ requires C, 78·5; H, 3·4; N, 13·1%).

2'' : 3'-*Diamidino*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—The corresponding dicyanide (6·4 g., above) was suspended in a mixture of dry ethanol (7 c.c.) and dry nitrobenzene (20·8 c.c.) and saturated with dry hydrogen chloride at 0°. A homogeneous solution was obtained after 24 hours at room temperature, and after a further 24 hours there was a fine yellow precipitate, and dry ether was added to complete the separation of the ethyl imidate hydrochloride. The solid was shaken with 10% alcoholic ammonia (68 c.c.) and after 3 days the solid was removed, the filtrate was evaporated to dryness under reduced pressure at room temperature, and the residue was dissolved in water (8 c.c.) and acidified with hydrochloric acid. The pale cream-coloured solid (3 g., 32%), m. p. 285—288°, was purified by reprecipitation from alcohol with dry ether and recrystallisation from 2N-hydrochloric acid. The *amidine dihydrochloride dihydrate* had m. p. 290—293° (Found: N, 14·8; Cl', 15·1; H_2O, 7·5. $C_{21}H_{17}ON_5,2HCl,2H_2O$ requires N, 15·1; Cl', 15·4; H_2O, 7·8%).

2''-*Amidino*-5-p-*amidinophenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—This amidine was obtained in 25% yield from the corresponding dicyanide by the method used in the case of the isomeric compound. The *amidine dihydrochloride hydrate*, crystallised from dilute hydrochloric acid, had m. p. 280—283° (Found: loss at 100°/vac., 9·4. Found, on dried material: C, 58·3; H, 4·7; N, 16·3. $C_{21}H_{19}ON_5Cl,2\frac{1}{2}H_2O$ requires H_2O, 9·5. $C_{21}H_{19}ON_5Cl$ requires C, 58·9; H, 4·4; N, 16·4%).

Alkaline Fission of 2'' : 3'-*Dicyano*-5-*phenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—Sodium (4 g., 8·7 atomic proportions) was slowly added to a suspension of the dicyanide (6·4 g.) in boiling absolute alcohol (120 c.c.), the mixture was boiled for another 2 hours, and the resulting red-brown solution was worked up by one of the following methods. (*a*) The solution was neutralised at 0° with an equivalent of 36% hydrochloric acid, and sodium chloride was then removed; the filtrate, concentrated to 1/3 vol. under reduced pressure, gave 5-*cyano*-2-*ethoxybenzophenone* (35·5%), m. p. 101—102·5° or 104—105° after several crystallisations from alcohol (Found: C, 76·2; H, 5·0; N, 5·7. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). This cyanide was also obtained from the corresponding amide (0·4 g.) and boiling acetic anhydride (5 c.c.). (*b*) Water (50 c.c.) was added, the mixture was concentrated to crystallising point, then cooled, and the yellow sodium salt (A) collected and neutralised with 2N-hydrochloric acid, giving a solid which was recrystallised from alcohol. The solution deposited a crop of crystals immediately and a second solid separated from the filtrate after several days. The former were recrystallised from ethanol giving colourless needles of 5-*carbamyl*-2-*ethoxybenzophenone* 5-*cyano*-2-*hydroxyphenylimine*, m. p. 209—210° (Found: C, 72·5; H, 5·0; N, 11·1. $C_{23}H_{19}O_3N_3$ requires C, 71·7; H, 4·9; N, 10·9%). The second solid (above) was 5-*carbamyl*-2-*ethoxybenzophenone*, m. p. 157—158° [Found: C, 71·55; H, 5·55; N, 5·2; OEt, 15·95%; *M* (Rast), 279. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2; OEt, 16·7%; *M*, 269]. The yellow sodium salt (A) also gave this amide, m. p. and mixed m. p. 157—158° (33·6%), when it was boiled with dilute hydrochloric acid. The amide afforded a 2 : 4-dinitrophenylhydrazone, m. p. 258—264°, was dehydrated by acetic anhydride to the corresponding cyanide (above), and when it (0·2 g.) was boiled for 5 hours with 5N-sodium hydroxide (5 c.c.) it gave 5-*carboxy*-2-*ethoxybenzophenone*, m. p. 176—177° (Found: C, 71·15; H, 5·5. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). This acid (18·5%) was also obtained when the filtrate from the yellow sodium salt (A)

was acidified with concentrated hydrochloric acid, and was synthesised from 2-hydroxy-5-methylbenzophenone (Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56). This phenol (11 g.), sodium ethoxide solution [from sodium (1·2 g., 1 atom) and absolute alcohol (50 c.c.)], and ethyl bromide (4·6 c.c., 1·2 mols.) were boiled for 4 hours and afforded 2-ethoxy-5-methylbenzophenone (55%), m. p. 44—45° (Found: C, 79·7; H, 6·5. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). Auwers (*loc. cit.*) records m. p. 68°. When this ether (17 g.), potassium permanganate (30 g., equiv. to 4O), and water (350 c.c.) were stirred and heated on the steam-bath for 5 hours, part (6 g.) was recovered and part oxidised to 5-carboxy-2-ethoxybenzophenone (1·1 g.), m. p. and mixed m. p. 176—177° (Found: C, 71·3; H, 5·1%).

3′-*Nitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenz*-1-*oxa*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene and Methyl Sulphate* [Experiments by Dr. A. E. S. FAIRFULL].—The nitro-compound (1·8 g.) and methyl sulphate (3 c.c., 6·4 mols.) were boiled for 10 minutes, benzene was then added, and the resulting brown gum was triturated with ether and dissolved in hot methanol. On being cooled the solution deposited an orange solid (1·3 g., 66·5%), m. p. 149—151°, which on further crystallisation gave orange-red prisms of 2-(2-*methylamino*-4-*nitrophenoxy*)-4′-*nitrobenzophenone*, m. p. 152—153° (Found: C, 60·9; H, 3·9; N, 10·7. $C_{20}H_{15}O_6N_3$ requires C, 61·1; H, 3·8; N, 10·7%). Brady's reagent (in sulphuric acid) afforded the 2 : 4-*dinitrophenylhydrazone* which separated from glacial acetic acid in orange prisms, m. p. 234—235° (Found: N, 17·2. $C_{26}H_{19}O_9N_7$ requires N, 17·1%). The amino-ketone afforded a white *hydrobromide*, m. p. 200—202° (Found: N, 9·1. $C_{20}H_{16}O_6N_3Br$ requires N, 8·9%), and a sulphate, m. p. 191—192°; the free base was regenerated from both these salts by warm water.

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221. *The Formation of* 1 : 2-7 : 8-*Diphthaloylcarbazole by Dehydrogenation of* 1 : 1′-*Dianthraquinonylamine.*

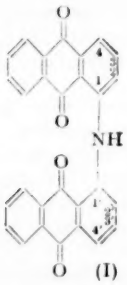
By WILLIAM BRADLEY and COLIN R. THITCHENER.

Whilst the action of fused alkali hydroxides on 6 : 6′-di*meso*benzanthronylamine leads to hydrolysis and formation of 6-hydroxy*meso*benzanthrone, both 1 : 2′- and 2 : 2′-dianthraquinonylamine yield alizarin as the main product. In these instances hydroxylation precedes hydrolysis. 1 : 1′-Dianthraquinonylamine behaves otherwise. Hydroxylation and hydrolysis proceed only in minor degree, the main reaction being cyclisation to 1 : 2-7 : 8-diphthaloylcarbazole. The further action of alkali on the product yields 1 : 2-phthaloylcarbazole and an acid from which carbazole results on heating with soda-lime. The cyclisation reaction requires the presence of two anthraquinone nuclei. Its rate depends on the alkali employed. The mechanism of the reaction is considered to be analogous to the formation of di*meso*benzanthronyl from *meso*benzanthrone and of di-(1 : 9-pyrazoloanthron-2-yl) from 1 : 9-pyrazoloanthrone. The identity of the products obtained by heating 1 : 1′-dianthraquinonylamine with potassium hydroxide and with aluminium chloride is confirmed.

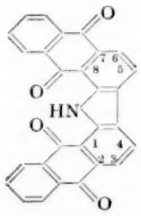
IN earlier communications an account has been given of the self-coupling of *meso*benzanthrone, three isomeric benzo*meso*benzanthrones, pyridino*meso*benzanthrone and 1 : 9-pyrazoloanthrone by processes of dehydrogenation brought about by alkalis (Bradley and Jadhav, *J.*, 1948, 1622; Bradley and Sutcliffe, *J.*, 1952, 1247, 2118; Bradley and Geddes, *J.*, 1952, 1636). The present investigation is concerned with the analogous conversion of 1 : 1′-dianthraquinonylamine (I) into 1 : 2-7 : 8-diphthaloylcarbazole (II), in which, as in the examples given, two aromatic nuclei become united through carbon atoms situated *para* to carbonyl groups.

Early work (D.R.-P. 230,407, 240,080, 251,021; 262,788) indicated that alkali and aluminium chloride converted 1 : 1′-dianthraquinonylamine into indanthrone derivatives, but further investigation (D.R.-P. 267,522; 267,833) showed that the yellow product was, in both cases, more probably 1 : 2-7 : 8-diphthaloylcarbazole (II).

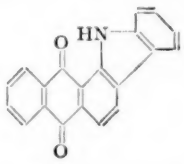
In the present work, (I) was first heated with aluminium chloride by the method given in B.I.O.S. Final Report, No. 1493, p. 53 (London, H.M.S.O.). The product, which had the properties recorded in the literature, was further characterised by its absorption spectrum in sulphuric acid (see Figure). For the potassium hydroxide fusion, it was



(I)

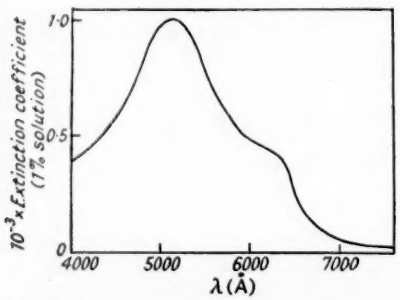


(II)



(III)

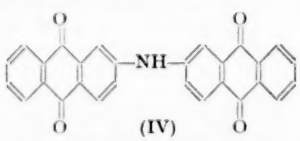
found that at 220° the main product was yellow-brown, as described in D.R.-P. 230,407, and that crystallisation followed by sublimation gave a bright yellow colouring matter having the same absorption spectrum in sulphuric acid as that obtained by use of aluminium



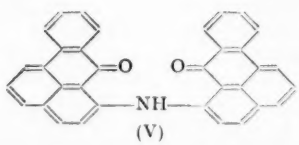
Absorption spectrum of a 0·001% solution of 1 : 2-7 : 8-diphthaloylcarbazole in concentrated sulphuric acid.

chloride. Other products of this reaction were 1 : 2-phthaloylcarbazole (III), anthraquinone, a trace of alizarin, and an acid which gave carbazole when heated with soda-lime.

The correctness of the constitution (II) assigned to the main product was confirmed by further heating of the purified material with potassium hydroxide at 220°; 1 : 2-phthaloylcarbazole (III) was formed, with an acid derived from carbazole. From this experiment it is probable that (III), when formed by the alkali fusion of (I), is derived by the decomposition of (II).



(IV)



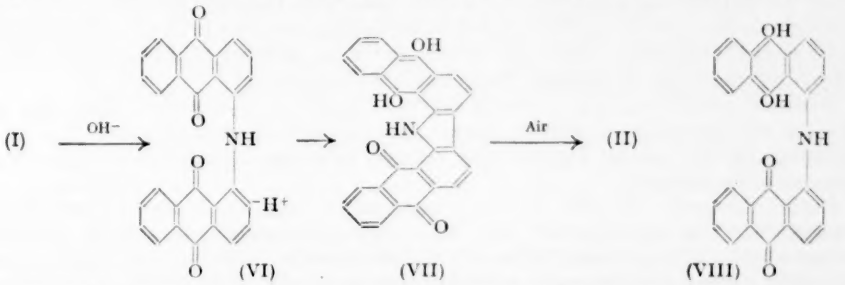
(V)

In yielding a carbazole derivative as the main product of alkali fusion (I) differs markedly from both 1 : 2′- and 2 : 2′-dianthraquinonylamine (IV) which under similar conditions yield alizarin and ammonia but no derivative of carbazole. It also differs from 6 : 6′-di*meso*benzanthronylamine (V) which, even with amyl-alcoholic potassium hydroxide, is readily hydrolysed to 6-amino- and 6-hydroxy-*meso*benzanthrone (Bradley, *J.*, 1948, 1175).

A further study of 2 : 2′-dianthraquinonylamine showed that indanthrone was absent from the product of alkali fusion, an indication that, unlike (V), the amine did not undergo initial hydrolysis to 2-hydroxy- and 2-amino-anthraquinone (for the conversion of 2-amino-anthraquinone into indanthrone see D.R.-P. 129,845 and Bradley and Leete, *J.*, 1951, 2129). It is probable that, like 2-anilinoanthraquinone (Bradley and Leete, *loc. cit.*),

2 : 2′-dianthraquinonylamine is first hydroxylated in the 1-position, and subsequently hydrolysed to give alizarin.

In the conversion of (I) into (II) the product is initially obtained in the form of an alkali-soluble reduction product from which (II) is precipitated on aeration. These changes are consistent with the following scheme (cf. Bradley and Geddes, *loc. cit.*).



It should be mentioned that the cyclisation of (I) to (II) is dependent on the presence of two quinone nuclei. Neither 1- nor 2-anilinoanthraquinone yields a carbazole derivative on fusion with alkali.

The formation of anthraquinone as a by-product of the reaction is of interest. It is possible that the intermediate (VII) reduces some of the starting material to (VIII), from which anthraquinone results by elimination of 1-aminoanthraquinone. Such a reaction would be analogous to the fission of 2-amino-1 : 2′-dianthraquinonylamine following reduction (Bradley and Leete, *J.*, 1951, 2160).

Cyclisation of (I) to (II) also occurs when sodium hydroxide replaces potassium hydroxide. At 220° the reaction proceeds much more slowly, but at 280° sodium hydroxide is as effective as potassium hydroxide at the lower temperature. Cæsium hydroxide, however, is as effective as potassium hydroxide. Thus the basic strength of the condensing agent is a factor in the cyclisation. The addition of a small proportion of phenol facilitates cyclisation by promoting adequate mixing, the composition of the product remaining substantially unaltered.

Attempts to prepare the *N*-methyl derivative of (I) were unsuccessful. It was hoped to employ it to establish whether the free –NH– group of (I) plays an essential part in the ring-closure : this appeared improbable since in the case of 1 : 9-pyrazoloanthrone sodium anilide causes the union of two nuclei whether the starting material is *N*-methylated or not (Bradley and Geddes, *loc. cit.*). The difficulty in methylating (I) is doubtless related to its stability as a molecule. It does not easily form a potassium derivative when methanolic potassium hydroxide is added to its solution in pyridine. 2 : 2′-Dianthraquinonylamine on the contrary readily forms a potassium salt, and *N*-methylation presents no difficulty (Bradley and Leete, *J.*, 1951, 2138).

The occurrence of hydroxylation with (IV) and of cyclisation with (I) provides a further illustration of the close connection between hydroxylation and self-coupling processes brought about by alkali hydroxides. Both reactions are theoretically possible with (I) and (IV) and it is probable that the result is determined by their relative rates in the two instances. A similar relation has been observed for 1- and 2-hydroxyanthraquinone. The first yields 1 : 1′-dihydroxy-2 : 2′-dianthraquinonyl (Scholl, Schwinger, and Dischendorfer, *Ber.*, 1919, **52**, 2254) whilst the second gives mainly alizarin (Liebermann, *Ber.*, 1871, **4**, 108; Baeyer and Caro, *ibid.*, 1874, **7**, 968). In the present work 1-aminoanthraquinone gave a product which could not be identified; it did not contain more than a trace of alizarin. 1-Anilinoanthraquinone gave alizarin but much of the product was recovered unchanged; both 2-amino- and 2-anilino-anthraquinone afford 1-hydroxy-derivatives (Bradley and Leete, *loc. cit.*). Hydroxylation in the 1-position is thus a common reaction with 2-derivatives of anthraquinone but an analogous reaction occurs less readily with the isomeric 1-substituted compounds. The difference in ease of substitution, which is determined by the difference in nuclear reactivity in the two series, may have its origin in

a difference of structure, the 1-derivatives (less reactive) approaching typical aromatic forms more closely. From this point of view it is the difficulty of hydroxylating (I) that allows coupling through the 2- and 2′-positions.

The cyclisation of (I) to (II) by means of aluminium chloride (B.I.O.S., *loc. cit.*) was studied in detail. Neither alizarin nor 1 : 2-phthaloylcarbazole was obtained at 140°; at 250° the product contained (II), but little or none of its reduced form (VII). 1 : 2-7 : 8-Diphthaloylcarbazole was readily isolated by subliming the crude product or by extracting it with methyl phthalate. There was no evidence of the presence of reduced forms capable of dehydrogenation by azobenzene, methylene-blue, or bromanil.

When aluminium chloride is used it is probable that the cyclisation follows the same course as with potassium hydroxide, except that the electron-seeking carbon atom at the 2′-position (see VI) results from valency changes following co-ordination of the oxygen atoms with the catalyst.

During the work a number of related matters were studied. Scholl, Schwinger, and Dischendorfer (*loc. cit.*) showed that 1-hydroxyanthraquinone, a possible hydrolysis product of (I), yields a reduced form of 1 : 1′-dihydroxy-2 : 2′-dianthraquinonyl on fusion with alkali. These reactions were confirmed, also conversion of the product into 1 : 2-7 : 8-diphthaloyldibenzofuran. None of these three compounds was found in the crude product obtained by heating (I) with potassium hydroxide, an indication that in this reaction, hydrolysis, if it occurs, is not an important step. It was also observed that sodium hydroxide was much less effective than potassium hydroxide in the self-condensation of 1-hydroxyanthraquinone.

In attempts to prepare *N*-methylated substitution products of (I), 2-nitro- and 4 : 4′-dinitro-1 : 1′-dianthraquinonylamine (D.R.-P. 254,186) were prepared. Both were stronger acids than (I) and readily gave characteristic colour reactions with methanolic potassium hydroxide in pyridine, but neither these nor (V) could be methylated with potassium carbonate and methyl toluene-*p*-sulphonate in trichlorobenzene. 1-Methylaminoanthraquinone did not condense with 1-chloro-2-nitroanthraquinone in the absence of a catalyst. With potassium acetate and cuprous chloride in nitrobenzene 1-methylaminoanthraquinone and 1-chloroanthraquinone afforded (I), demethylation having occurred (Bradley and Leete, *J.*, 1951, 2147).

Experimental

Action of Potassium Hydroxide on 2 : 2′-Dianthraquinonylamine.—(*a*) 2 : 2′-Dianthraquinonylamine (2·0 g.) was added at 180° to potassium hydroxide (20 g.) and water (2 c.c.). The temperature was raised to 220° during 30 minutes. A purple colour developed and ammonia was liberated. After 15 minutes longer the melt was added to water (200 c.c.), and the suspension was aerated for 24 hours. Filtration gave a purple solution from which a brown solid (1·8 g.) separated on the addition of acid. On sublimation it gave alizarin, 2 : 2′-dianthraquinonylamine, and a small amount of a black, non-volatile product. A similar result was obtained when the fusion was carried out in the presence of phenol (0·2 g.); in this case sublimation of a portion *in vacuo* gave alizarin (0·017 g.), 2 : 2′-dianthraquinonylamine (0·041 g.), and residue (0·012 g.).

(*b*) 2 : 2′-Dianthraquinonylamine (4 g.) was added to potassium hydroxide (50 g.) and water (5 c.c.) at 200°, and the temperature was raised slowly to 230—240° and maintained for 30 minutes. Ammonia was liberated and a violet melt resulted. This was added to water (500 c.c.), heated to boiling, and aerated for 12 hours, and the purple solution filtered from a blue residue. The filtrate afforded 2·7 g. of alizarin, and no other product could be detected by sublimation or chromatography from chlorobenzene on alumina. The blue residue (1·0 g.; m. p. 480—500°) gave a solution of the same colour in concentrated sulphuric acid. In pyridine it gave an orange solution, changed to bright green on the addition of methyl-alcoholic potassium hydroxide, and this remained stable on the further addition of a small volume of water or a considerable volume of alcohol. Much water caused the restoration of the original orange colour. Sublimed from a bath at 380—400°/0·5 mm. the blue product gave 2 : 2′-dianthraquinonylamine, a trace of alizarin, and a small non-volatile residue, only a small portion of which dissolved in warm alkaline dithionite solution. There was no evidence of the presence of indanthrone. The presence of alizarin and 2 : 2′-dianthraquinonylamine in the crude

product and the absence of indanthrone were confirmed by extraction with warm alkaline dithionite and chromatography of the resulting solution on cellulose.

Action of Potassium Hydroxide on 1 : 2′-*Dianthraquinonylamine.*—(*a*) 1 : 2′-Dianthraquinonylamine (1·0 g.) was added at 180° to potassium hydroxide (10 g.) and water (1 c.c.). The temperature was then raised to 220° during 30 minutes, and maintained for 20 minutes. The violet product was added to water (250 c.c.), and the resulting suspension was heated to boiling and aerated for 6 hours. It was acidified and the brown precipitate (1·0 g.) collected, washed, and dried. Sublimation of 0·082 g. at 140—150°/1 mm. for 3 hours gave alizarin (0·017 g.) and further sublimation at 360°/1 mm. gave unchanged 1 : 2′-dianthraquinonylamine (0·050 g.). There was a non-volatile residue (0·011 g.) which was insoluble in warm alkaline dithionite solution.

(*b*) The foregoing experiment was repeated with the addition of phenol (0·3 g.) to the alkali melt. After 45 minutes at 220° the products obtained when a portion was heated *in vacuo* were alizarin (0·045 g.), 1 : 2′-dianthraquinonylamine (0·019 g.), and a non-volatile residue, insoluble in alkaline dithionite solution (0·020 g.).

Action of Potassium Hydroxide on 1 : 1′-*Dianthraquinonylamine.*—(*a*) 1 : 1′-Dianthraquinonylamine (5 g.) was added to potassium hydroxide (50 g.) and water (5 c.c.) and heated as described in D.R.-P. 230,407. The brown melt was added to water (500 c.c.), heated to boiling, aerated for 12 hours, and then filtered; it afforded a brown solid (A) (4·4 g.) and a violet solution. The solution on acidification gave a gelatinous, brown precipitate (0·2 g.), and this on washing, drying, dissolving in chlorobenzene, and chromatography on alumina gave four bands. The most strongly absorbed was dark brown. It was followed by a bluish-red zone, and this on extraction with acetic acid gave orange-brown needles of alizarin, m. p. and mixed m. p. 284—286°. The solid (A) decomposed at >400°. Crystallisation from diethyl phthalate gave orange needles. Sublimation of (A) at 360—380°/0·2—0·4 mm. gave five zones. The most volatile product, pale yellow needles, crystallised from acetic acid as colourless needles, m. p. 282°, not depressed on admixture with anthraquinone, m. p. 283°, and having the properties thereof. The next zone was red and very small. The adsorbed colouring matter was insoluble in 5% potassium hydroxide, gave an orange solution in alkaline sodium dithionite, and dissolved in concentrated sulphuric acid with a yellow brown colour, and in pyridine forming a red solution which remained unaltered on the addition of methanolic potassium hydroxide. The third zone consisted of orange needles, m. p. 249—250°, not depressed on admixture with 1 : 2-phthaloylcarbazole, m. p. 251°. It gave a deep blue solution in concentrated sulphuric acid, changing to purple on warming. It dissolved in pyridine with a golden-yellow colour, changing to deep green on the addition of methanolic potassium hydroxide; the green colour was stable towards the addition of a small proportion of water, but further dilution regnerated the initial yellow colour. The fourth zone consisted of 1 : 1′-dianthraquinonylamine. The fifth band consisted of a dense mass of yellow needles of 1 : 2-7 : 8-diphthaloylcarbazole, very sparingly soluble in pyridine. It gave a red solution in concentrated sulphuric acid the absorption spectrum of which was identical with that of the compound described in B.I.O.S. Final Report No. 1493, p. 53 (Figure). It decomposed without melting at >400°. The residue from the sublimation of (A) was partly soluble in chlorobenzene. The resulting green solution, chromatographed on alumina, gave two bands. The more strongly adsorbed was black; elution with pyridine gave a green solution which became purple on the addition of methanolic potassium hydroxide.

A repetition of the sublimation of a portion of (A) at 380—400°/0·5 mm., grinding the residue and again subliming, it gave the following yields: anthraquinone (0·0016 g.), unidentified red compound (0·0006 g.), 1 : 1′-dianthraquinonylamine (0·0089 g.), 1 : 2-phthaloylcarbazole (0·0029 g.), 1 : 2-7 : 8-diphthaloylcarbazole (0·0278 g.), and residue (0·0261 g.).

(*b*) 1 : 1′-Dianthraquinonylamine (2·0 g.), potassium hydroxide (20 g.), water (2 c.c.), and phenol (0·5 g.) heated and further treated as in (*a*) gave a brown solid (1·7 g.) which resembled (A) in composition. Vacuum-sublimation gave anthraquinone (0·0011 g.), unidentified red compound (0·0005 g.), 1 : 1′-dianthraquinonylamine (0·0008 g.), 1 : 2-phthaloylcarbazole (0·0016 g.), 1 : 2-7 : 8-diphthaloylcarbazole (0·0273 g.), and residue (0·0231 g.).

(*c*) Experiment (*b*) was repeated with the addition of zinc dust (0·75 g.) and omission of the phenol. Almost none of the product was soluble in aqueous potassium hydroxide (absence of alizarin) and on sublimation the sublimate was almost pure 1 : 1′-dianthraquinonylamine. Only a trace of diphthaloylcarbazole was present.

(*d*) 1 : 1′-Dianthraquinonylamine (5 g.) was recovered (4·6 g.) almost entirely unchanged after being heated with sodium hydroxide (50 g.) and water (5 c.c.) at 220° for 15 minutes;

alizarin was formed in very small amount. The same result was obtained when 1 : 1′-dianthraquinonylamine (0·2 g.), sodium hydroxide (2 g.), water (0·5 c.c.), and phenol (0·5 g.) were heated together at 220° for 30 minutes, and again when the last experiment was repeated with the addition of sodium chloride (cf. D.R.-P. 175,626). There was no formation of 1 : 2-7 : 8-diphthaloylcarbazole in any of these experiments.

(*e*) 1 : 1′-Dianthraquinonylamine (5 g.), heated at 220° for 5 hours with sodium hydroxide (50 g.), water (5 c.c.), and phenol (0·5 g.), with the addition of small successive amounts of water to keep the melt fluid, gave an acid (alizarin?), which dissolved in alkali with a violet colour, and a black alkali-insoluble solid (4·2 g.). After washing, drying, and heating at 440°/0·1 mm. a portion of the black solid yielded the following products: anthraquinone (0·0033 g.), 1 : 1′-dianthraquinonylamine (0·0014 g.), 1 : 2-phthaloylcarbazole (0·0048 g.), 1 : 2-7 : 8-diphthaloylcarbazole 0·0014 g.), and unsublimed residue (0·087 g.).

(*f*) Heated with sodium hydroxide (20 g.) and water (5 c.c.), 1 : 1′-dianthraquinonylamine (2 g.) remained largely unaltered until the temperature reached 250—260°. After 20 minutes at 280° 1·2 g. of product was obtained on addition to water. Sublimation of a portion gave anthraquinone (0·0018 g.), 1 : 1′-dianthraquinonylamine (0·0116 g.), 1 : 2-phthaloylcarbazole (0·003 g.), 1 : 2-7 : 8-diphthaloylcarbazole (0·0098 g.), and residue (0·0162 g.).

Degradation of 1 : 2-7 : 8-*Diphthaloylcarbazole by Potassium Hydroxide.*—(*a*) 1 : 2-7 : 8-Diphthaloylcarbazole (2 g.) was added to potassium hydroxide (20 g.) and water (2 c.c.) at 170—180° and then the temperature was raised to 220° during 30 minutes. After 15 minutes at 220° the melt was added to water (500 c.c.) and the yellow-brown solid was collected, and washed with 1% potassium hydroxide solution, and then with water. Finally it was dried (1·8 g.) and a portion was sublimed at 360—380°/0·5 mm. for 12 hours. The most volatile product was 1 : 2-phthaloylcarbazole (0·030 g.; m. p. 249—253°), identical with the compound prepared from 1-chloroanthraquinone and benzotriazole according to Ullmann and Illgen (*Ber.*, 1914, **47**, 380). 1 : 2-7 : 8-Diphthaloylcarbazole (0·001 g.) also sublimed; there was a non-volatile residue (0·009 g.).

(*b*) 1 : 2-7 : 8-Diphthaloylcarbazole (2 g.) was added to potassium hydroxide (40 g.) and water (4 c.c.) at 220°, and the mixture was stirred whilst the temperature was raised to 320° during 1 hour. Initially the reactants formed a yellow suspension, but the colour changed slowly to green. Finally a dark brown solution resulted. At this stage all the diphthaloylcarbazole, which was readily detected because it dissolved in alkaline dithionite solution with a red colour, had been decomposed. The product was added to water and the solution was filtered and acidified. A precipitate formed and this was collected, washed, and dried (0·75 g.). It was soluble in aqueous potassium carbonate. Heated with 200-mesh calcium oxide (7 g.) it yielded a sublimate of white plates, which, after collection, washing, and drying, had m. p. 226—230° (0·2 g.). Recrystallisation from aqueous alcohol gave the pure compound, m. p. 233—235°, not depressed by admixture with carbazole, m. p. 235—236°. It gave a green colour with sodium nitrite and concentrated sulphuric acid.

Fusion of 1 : 1′-*Dianthraquinonylamine with Cæsium Hydroxide.*—Aqueous solutions of cæsium sulphate (1·07 g.) and barium hydroxide (0·472 g.) were mixed, the precipitated barium sulphate removed, and the filtrate evaporated to dryness. Water (0·2 c.c.) was added to the residue and the resulting solution was heated to 150°. At this temperature 1 : 1′-dianthraquinonylamine (0·04 g.) was added. The mixture was then held at, successively, 150° (10 minutes), 160° (10 minutes), 200° (20 minutes). The product consisted of unaltered 1 : 1′-dianthraquinonylamine. In a second experiment 1 : 1′-dianthraquinonylamine (0·04 g.) was added to a similar preparation of cæsium hydroxide at 180°. The temperature was raised slowly to 220° and maintained for 20 minutes. Added to water (100 c.c.) the melt dissolved forming a brown solution. This was aerated for 4 hours and the brown precipitate was collected, washed, and dried (0·02—0·03 g.). Sublimation at 360°/0·5—1·0 mm. gave 1 : 2-7 : 8-diphthaloylcarbazole as the main product. Traces of 1 : 2-phthaloylcarbazole and 1 : 1′-dianthraquinonylamine were also present.

Action of Fused Potassium Hydroxide on 6 : 6′-*Dimesobenzanthronylamine.*—(*a*) Finely powdered 6 : 6′-di*meso*benzanthronylamine (1·0 g.) was added to potassium hydroxide (10 g.) and water (1 c.c.) at 180°. The temperature was raised slowly to 220°. Ammonia was evolved, vigorously at 220°. The reaction ceased after 25 minutes and the product was added to water. The suspension was acidified and the greenish-yellow solid was collected, washed, and dried (0·91 g.). Crystallised from benzene and then from acetic acid it gave needles, m. p. 176°, not depressed by admixture with 6-hydroxy*meso*benzanthrone, m. p. 177—178°.

(*b*) 6 : 6′-Di*meso*benzanthronylamine (4·0 g.) was added to potassium hydroxide (200 g.)

and water (20 g.) at 200°. The temperature was raised to 280° during an hour and then the product was isolated. It was a greenish-yellow solid (3·5 g.) which consisted of 6-hydroxy*meso*-benzanthrone (2·4 g.) and benzene-insoluble material (0·91 g.). The latter did not sublime at 360—400°/0·5—1·0 mm.; it decomposed above 400°.

Potassium Hydroxide Fusion of 1-*Aminoanthraquinone.*—The 1-aminoanthraquinone was first crystallised as the sulphate from sulphuric acid and then chromatographed from chlorobenzene on alumina. The amine (5 g.) was added to a melt of potassium hydroxide (50 g.) and water (5 c.c.) at 150°. The temperature was raised to 220° during 30 minutes and maintained for 15 minutes longer. The product added to water gave a brown suspension, and this was aerated for 24 hours. The dark brown precipitate (A) (4·6 g.; m. p. >360°) was separated from the solution which was then acidified. The resulting small precipitate was collected, washed, dried, dissolved in chlorobenzene, and then chromatographed on alumina. Three zones formed. The middle brick-red zone, extracted with acetic acid, gave orange needles, m. p. 288°, not depressed on admixture with alizarin. The product (A) extracted with acetic acid gave a deep green solution from which a blue solid (2·5 g.) separated on addition to water. The blue product extracted with chlorobenzene gave 1-aminoanthraquinone (0·5 g.; m. p. 252—253°), not depressed on admixture with authentic material. Prolonged extraction with chlorobenzene gave a green solution and this was chromatographed on alumina at 110°. Several zones formed; the main one was black and was the most strongly retained. The black zone extracted with acetic acid gave a solution from which a green precipitate (Found: C, 74·6; H, 3·2; N, 2·9%) (1·7 g.), m. p. 400°, separated on addition to water. This dissolved in concentrated sulphuric acid forming a red solution which became orange on the addition of a drop of formaldehyde solution but remained unchanged on addition of boric anhydride. The green substance dissolved in pyridine with the same colour; a purple colour developed on the addition of a drop of methyl-alcoholic potassium hydroxide, and the original colour was regenerated on further addition of water. It did not dissolve in 5% potassium hydroxide but a brown solution resulted on the addition of sodium dithionite; aeration reprecipitated the green substance. It was not affected by heating with acetic anhydride.

Potassium Hydroxide Fusion of 1-*Anilinoanthraquinone.*—1-Anilinoanthraquinone (5 g.) was added to potassium hydroxide (50 g.) and water (5 c.c.) at 170°. The temperature was raised slowly to 220° and maintained for 10 minutes. The black semi-solid product was added to water (200 c.c.), and the suspension was heated to boiling and aerated for 6 hours. Filtration afforded a purple solution and a solid. Acidification of the solution gave 0·85 g. of alizarin, m. p. 282—285° (288° after recrystallisation). Extraction of the solid with alcoholic potassium hydroxide solution gave an additional quantity of alizarin and a purple residue, melting range 120—140°. Crystallisation from alcohol gave unchanged 1-anilinoanthraquinone, m. p. 143—145°. Sublimation at 250°/0·1 mm. before crystallisation gave a trace of alizarin; 1 : 2-phthaloylcarbazole was absent.

Action of Aluminium Chloride on 1 : 1′-*Dianthraquinonylamine* (cf. B.I.O.S., *loc. cit.*).—An intimate mixture of anhydrous aluminium chloride (60 g.), 1 : 1′-dianthraquinonylamine (30 g.), and sodium chloride (7·5 g.) was heated at 165° for an hour and then at 250° for 30 minutes. The cooled product, added to water and heated with hydrochloric acid, gave 28 g. of insoluble black material (A), which still contained a small proportion of an aluminium compound (Found, in residue after further heating for 2 hours with hot, concentrated hydrochloric acid: Al, 0·3%). (A) adsorbed methylene-blue from an aqueous solution but did not reduce it. It did not reduce azobenzene at 100° (30 hours) or at 200° (6 hours), or bromanil in boiling acetic acid (3 hours). With a 5·14% solution of iodine in boiling benzene it gave a brownish-yellow product, not containing iodine. Heated with alkaline sodium hypochlorite, then with nitrobenzene, sodium hypochlorite, and potassium permanganate as described in the B.I.O.S. Report, 19 g. of (A) afforded a yellow product (8·5 g.). Crystallisation from nitrobenzene gave small, golden-yellow needles, which decomposed when heated above 400° and gave the same colour and absorption spectrum in concentrated sulphuric acid as the product obtained by the fusion of 1 : 1′-dianthraquinonylamine with potassium hydroxide (Figure).

Sublimed for 2 hours from a bath at 360—380°/0·5—0·8 mm. (A) afforded a more volatile band consisting of a small amount of crystalline 1 : 1′-dianthraquinonylamine and a crop of yellow needles of 1 : 2-7 : 8-diphthaloylcarbazole. A separation carried out for 12 hours at 360° gave 1 : 2-7 : 8-diphthaloylcarbazole (43%), 1 : 1′-dianthraquinonylamine (1·1%), and unsublimed residue (48%).

Extracted with boiling dimethyl phthalate, (A) dissolved in part forming a yellow solution from which 1 : 2-7 : 8-diphthaloylcarbazole separated on cooling. The identity of the product

was confirmed by its absorption spectrum in sulphuric acid. Repeated extraction of (A) with dimethyl phthalate afforded a black, insoluble residue which did not dissolve in cold, concentrated sulphuric acid or in alkaline dithionite solution. Extracted for 12 hours with cold, concentrated sulphuric acid A (0·2962 g.) afforded 0·1430 g. (Found : C, 74·2; H, 3·6; N, 1·5%) of the residue.

Experiments on the Methylation of 1 : 1′-*Dianthraquinonylamine and its Derivatives.*—1 : 1′-Dianthraquinonylamine was recovered unaltered after 8 hours' heating with methyl toluene-*p*-sulphonate and potassium carbonate in *o*-dichlorobenzene. A similar results was obtained when the medium was mixed polychlorobenzenes, boiling range 220—240°, and the period of heating 48 hours.

4 : 4′-Dinitro-1 : 1′-dianthraquinonylamine was recovered mainly unchanged after 12 hours' heating in polychlorobenzenes with potassium carbonate and methyl toluene-*p*-sulphonate.

Similar negative results were obtained in attempts to *N*-methylate 2-*nitro*-1 : 1′-*dianthraquinonylamine*. This compound was prepared as follows.

1-Chloro-2-nitroanthraquinone (10 g.) and 1-aminoanthraquinone (10 g.) were heated under reflux in mixed polychlorobenzenes (80 c.c.; boiling range, 220—240°). Hydrogen chloride was liberated and the orange solution of the reactants slowly became dark bluish red. After 20 hours the product was cooled and added to alcohol (100 c.c.), and the red precipitate was washed with warm benzene. After further extraction with alcohol the residue (8 g.) crystallised from *o*-dichlorobenzene as bluish-red needles, m. p. 318° (Found : C, 70·8; H, 2·6; N, 5·6. $C_{28}H_{14}O_4N_2$ requires C, 70·9; H, 3·0; N, 5·9%). It dissolved in pyridine with a cherry-red colour changed to bright green on the addition of methyl-alcoholic potassium hydroxide. The green colour was stable towards the addition of a small proportion of water, but more water caused the regeneration ot the original red colour. It dissolved in concentrated sulphuric acid forming a bluish-green solution, changed to brown on the addition of boric acid, and rendered slightly bluer with formaldehyde. Heating for 30 minutes with alcohol containing 5% of hydrated sodium sulphide transformed 2-nitro-1 : 1′-dianthraquinonylamine into a blue product, m. p. >400°. This dissolved in alkaline dithionite forming a brown solution from which the original substance was reprecipitated on aeration. Contact with nitric acid rendered the blue compound yellow. Sublimed from a bath at 300—320°/1 mm. 2-nitro-1 : 1′-dianthraquinonylamine gave a purple product, m. p. 405—408° raised to 422—424° (Found : C, 72·0; H, 3·3; N, 4·7%) on crystallisation from pyridine. The purple solution in pyridine changed to pale blue on the addition of methyl-alcoholic potassium hydroxide.

1-Chloro-2-nitroanthraquinone (1·0 g.) and 1-methylaminoanthraquinone (1·0 g.) did not condense when heated in nitrobenzene (50 c.c.) for 20 hours. In the presence of cuprous chloride (0·5 g.) and potassium acetate (5·0 g.) 1-chloroanthraquinone (5·0 g.) and 1-methylaminoanthraquinone (5·0 g.) in nitrobenzene (50 c.c.) condensed with demethylation during 20 hours. The product (m. p. 378—381°; 8·4 g.) crystallised from the filtered nitrobenzene solution. The identity of the product with 1 : 1′-dianthraquinonylamine was confirmed by mixed m. p. and by the absorption spectrum in concentrated sulphuric acid.

6 : 6′-Di*meso*benzanthronylamine (1·0 g.) was recovered unaltered after 40 hours' heating with potassium carbonate (0·5 g.) and methyl toluene-*p*-sulphonate (2·0 g.) in *o*-dichlorobenzene (50 c.c.).

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222. *Passivity of Metals. Part XII.* Intense Attack at the Water-line of Otherwise Passive Metal.*

By A. M. Peers and U. R. Evans.

Intense water-line attack occurs on iron partly immersed in sodium chloride solution containing phosphate, carbonate, or other anodic inhibitor in certain proportions. This has been studied (1) in presence of oxygen without applied current and (2) in absence of oxygen with applied anodic current. Water-line attack does not depend on special surface conditions, acid constituents in the air, or evaporation. It is greatly affected by the shape of the meniscus crevice, and by the presence of films. The results support Schikorr's suggestion that water-line attack is due to slow replenishment of inhibitor in the meniscus. It is thus a form of crevice corrosion—analogous to that produced at contact with a glass rod.

Water-line attack arises in many ways. That met with on metal partly immersed in acid (Evans, *J. Inst. Met.*, 1923, **30**, 272; Hedges, *J.*, 1926, 832) may perhaps be due to preferential renewal of oxygen or removal of hydrogen at the water-line. The breakdown of passivity at the water-line on iron in concentrated nitric acid may be due either to preferential escape of nitrogen oxides so that the ratio $H_2O : N_2O_5$ may here reach the activation range (Evans, *J.*, 1927, 1036), or to autocatalysis connected with the retention of reduction products at the meniscus crevice (cf. Evans, *Trans. Faraday Soc.*, 1944, **40**, 120). The water-line trenching of steel in hard waters may be due to the acid constituents of the air interfering with the chalky film which protects the immersed portions.

The present paper deals with the intense water-line attack of iron in liquids containing sufficient inhibitor to passivate the immersed area. It can be observed in dilute sodium carbonate (or bicarbonate) solution in the absence of chlorides, but is most intense in carbonate–chloride or phosphate–chloride mixtures. If iron plates are immersed vertically in sodium chloride containing carbonate or phosphate, the area suffering corrosion shrinks as the carbonate or phosphate content increases; the attack becomes localized and usually intensified; finally, at high inhibitor concentration, attack ceases. The localized attack sometimes occurs at sheared edges or at surface defects, but is particularly associated with (1) the water-line and (2) crevices formed where the metal is in contact with a non-conducting solid, *e.g.*, a glass rod. The water-line attack is often so intense as to cause perforation of a steel plate within a time when the more general corrosion set up by inhibitor-free chloride solutions produces only slight thinning (Evans, *J. Soc. Chem. Ind.*, 1925, **44**, 163; 1927, **46**, 347). The intensification is partly caused by the dangerous combination of large cathode and small anode, but in some cases the total corrosion (as opposed to the intensity of corrosion) is increased by addition of inhibitor in inadequate amount (Mears and Evans, *Trans. Faraday Soc.*, 1935, **31**, 527). The deep trench, formed along the water-line, is closed in by a rust-box of triangular cross-section, bounded above by a curved rust membrane clinging to the meniscus, and below by a wall of looser rust which roughly constitutes a prolongation to the level portion of the water surface.

In chloride solution free from added inhibitor, the (cathodic) water-line zone is protected, partly at least because the cathode product (sodium hydroxide) is itself an inhibitor. When the liquid contains an added inhibitor, there is no reason for special immunity at the water-line, but the preferential attack at that level, and also at crevices formed by contact with glass, still requires explanation. Two explanations deserve consideration, as follows.

(1) *Exhaustion Theory.*—Protective films are believed to develop discontinuities at intervals (Britton and Evans, *J.*, 1930, 1777; Evans, *Nature*, 1946, **157**, 732); unless the inhibitor supply is sufficient to repair these breaks as they occur, attack will develop; since the rate of replenishment of inhibitor will be less at the tip of a meniscus, or in any other crevice, than elsewhere, attack is most probable at such places.

(2) *Rival-interface Theory.*—Matter which, in the fully immersed portion, would be

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deposited on the metal and would serve to repair discontinuities, may be deposited, for reasons of surface energy, upon the air–liquid or glass–liquid interface.

Mears and Evans (*Trans. Faraday Soc.*, 1934, **30**, 417) compared these two theories by studying crevices produced at contacts between steel rods and glass rods. Movement of the liquid was found to *decrease* the frequency of local attack—which clearly favours the exhaustion theory. The attack was found to be *more* frequent at crevices formed between two steel rods than at crevices between steel and glass—which is difficult to explain on the rival-interface theory, since there is no obvious reason why " repairing matter " should desert one steel surface for another.

The rival-interface theory was retained for water-line attack, where the membrane clinging to the curved liquid–air interface appeared to provide ocular evidence. It was felt that if, at one point on the water-line, anodic attack set in, the good supply of oxygen at cathodic points close to it would provide conditions favourable for continued attack. Another possible cause of attack was, however, advanced by Thornhill (*J. Iron Steel Inst.*, 1942, **146**, 94P), who found that water condensing on the dry metal ran down and diluted the concentration of inhibitor at the water-line.

Schikorr (personal communication, *ca.* 1938) argued that the meniscus was merely a special type of crevice and that water-line attack was due to exhaustion of inhibitor. Now the main difficulty to all exhaustion theories is that, although a crevice undoubtedly interposes a " resistance " on diffusion paths leading to points situated within it, yet it interposes a similar resistance on the current paths connecting the points (as anodes) to some large cathodic area situated outside the crevice; whatever the geometry of the crevice, it should multiply both resistances by the same factor. Presumably the film will only be kept in repair if the maximum rate of replenishment of inhibitor exceeds the maximum rate of production of metallic ions possible in inhibitor-free liquid (both rates being expressed in equivalents per unit time). Hence *in the absence of complications*, the inhibitor-requirements will be reduced by the crevice in the same proportion as the inhibitor-supply, and the probability of attack in the crevice should be the same as elsewhere.

It seemed desirable to decide whether water-line and ordinary crevice corrosion are really the same phenomenon, to study the effect of varying the shapes of the " meniscus crevice," and to enquire whether the presence of films (as one of the " complications " mentioned above) can remove the objections to the " exhaustion " theory.

Specimens of iron were partly immersed in chloride–phosphate solutions of different compositions, special attention being given to the effect of (1) surface condition of the metal, (2) acid constituents in the air, (3) slow evaporation which might alter the meniscus shape, (4) composition of the solution, (5) vertical dimensions of the specimen, (6) time of immersion, and (7) shape of the " crevice." The measurements included: (*a*) the loss of weight, after removal of corrosion product; (*b*) the " incidence " (*i.e.*, the mean fraction of the water-line attacked as measured on all the specimens); (*c*) the probability of water-line attack (*e.g.*, the proportion of specimens which developed it); (*d*) the probability of attack elsewhere.

These experiments (Series I) required to be performed in multiple, since, in any phenomenon depending on a *small* number of events, reproducibility may be expected to be poor (Evans, " Introduction to Metallic Corrosion," Arnold, 1948, p. 174). Hence simple methods were adopted.

Interpretation of experiments under " natural " conditions (*i.e.*, without electric current applied from an external source) is difficult owing to doubts as to the position and extent of the cathodic area on specimens developing a meniscus box. In inhibitor-free chloride, the cathodic area is usually a strip 2 mm. broad at the water line and this simple geometry facilitates interpretation (Evans and Hoar, *Proc. Roy. Soc.*, 1932, *A*, **137**, 358). For inhibitor-containing solutions, simplicity may best be achieved by abolishing the cathodic area on the specimen altogether, using a solution and gas-space quite free from oxygen, and producing corrosion by means of an applied current, with a platinum wire as cathode. Such experiments (Series II) gave results useful in interpreting those of Series I. In Series II, the method was more complicated, and the number of experiments smaller.

Experimental

Material and Procedure.—The steel used was cold-rolled sheet 0·03 cm. thick containing C 0·26, Mn 0·36, Si 0·207, S 0·031, P 0·038%; the surface was bright and rust-free, defective portions being discarded. Unless otherwise stated, the word "specimen" means a piece 2 × 6 cm. with the longer side parallel to the rolling direction, and carrying a 3 mm.-diameter hole at one end. Specimens were usually hung from a glass rod as in Fig. 1, but in Series I(3), the float shown in Fig. 2, was employed. The work was carried out in a room kept by thermostat at 25° ± 1°. Where loss of weight was required, the corrosion product was removed by 10 seconds' immersion in 20% sulphuric acid containing 0·1% of di-*o*-tolylthiourea, followed by rinsing with hot water and immediate drying with a clean towel.

All reagents, including the benzene used for degreasing, were of analytical reagent quality. For degreasing, two sets of 10 specimens, previously rinsed in benzene, wiped, and weighed, were strung on nichrome wire each separated from its neighbour by a glass bead, and were extracted with benzene for 2 hours (Soxhlet), and hung to dry for 15 minutes at 110°. All glass vessels used were cleaned in potassium chromate and sulphuric acid.

Series I.—(1) *Effect of surface condition.* Sixteen specimens were subjected to each surface treatment. They were weighed and placed at an angle of about 30° to the vertical, each in a 60-ml. beaker containing 30 ml. of solution. The beakers were placed under a bell jar on a shallow tray and set aside for 2 weeks. The tray was kept filled with water to minimize evaporation losses. The solutions contained sodium chloride (always 0·017M) and disodium

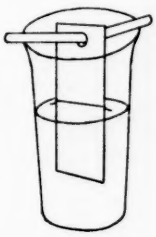


Fig. 1. *Partly immersed specimen.*

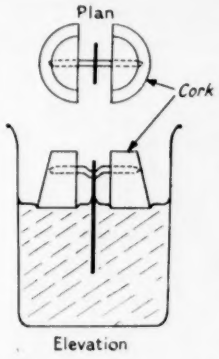


Fig. 2. *Buoy suspension, giving fixed water line.*

hydrogen phosphate of four concentrations (0·027, 0·034, 0·040, and 0·047M). Four specimens were tested in each mixture.

Each set of sixteen specimens received one of the following pre-treatments: (i) Wiping of the as-received surface with a dry cloth, to remove excess of oil used in packaging. (ii) Continuous washing with hot "AnalaR" benzene for 2 hours in a Soxhlet apparatus followed by 15 minutes' drying in air at 110°. (iii) Abrasion with "Oakeys" No. 1 cloth-backed emery. (iv) Abrasion with "Oakeys" No. 1 cloth-backed emery followed by benzene extraction as in (ii). (v) Rinsing in "AnalaR" benzene and annealing for 1 hour *in vacuo* at 950°.

After 2 weeks the specimens were freed from corrosion product and reweighed. The distribution of attack on each specimen was recorded. No serious differences were observed, although treatment (i) left a thin film of heavy oil on the specimen. Except for the most dilute concentration, the probability of water-line attack varied between 0·75 and 1·0, and the incidence between 0·4 and 0·6. The weight losses were least on specimens carrying oil films and greatest on annealed specimens.

(2) *Effect of acid constituents in the gas phase.* Ten specimens were cleaned with hot benzene, and tested when inclined at 30° in beakers, as already described. The solution contained sodium chloride (0·017M) and disodium hydrogen phosphate (0·040M). The beakers were placed in a large vacuum-desiccator containing concentrated potassium hydroxide solution. The desiccator was evacuated for 2 minutes with a rotary oil pump, then re-filled with air purified by passage through soda-lime, concentrated potassium hydroxide solution, and calcium chloride in that order. The above evacuation and re-filling was repeated three times.

After 2 weeks, every specimen had suffered attack at the water-line, the average incidence

being 0·68. The results differed little from those obtained in the presence of unpurified air. Water-line attack cannot be attributed to atmospheric impurities.

(3) *Effect of slow evaporation.* Ten cleaned specimens were set up in 400-ml. beakers

FIG. 3. *Weight loss in* 0·017M-NaCl *containing* NaOH.

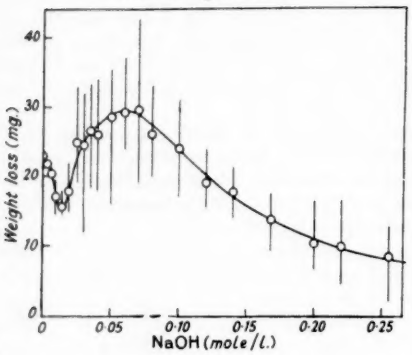


FIG. 4. *Weight loss in* 0·017M-NaCl *containing* Na_2CO_3.

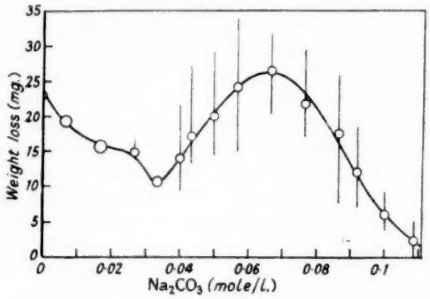


FIG. 5. *Weight loss in* 0·017M-NaCl *containing* Na_2HPO_4.

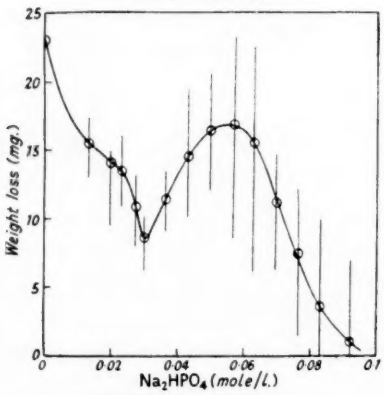


FIG. 6. *Weight loss in* 0·017M-NaCl *containing* K_2CrO_4.

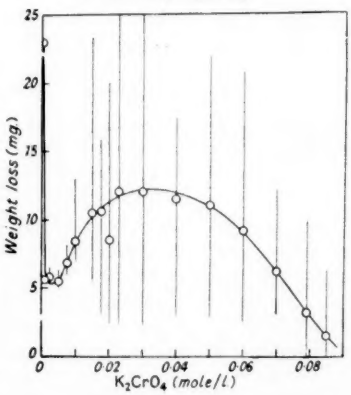
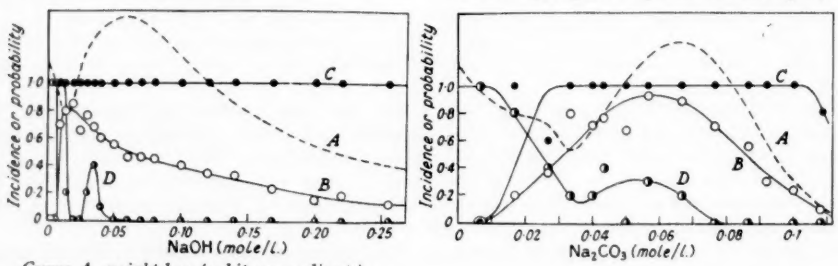


FIG. 7. *Water-line attack in* NaOH–NaCl *solutions.*

FIG. 8. *Water-line attack in* Na_2CO_3–NaCl *solutions (designation of curves as in Fig. 7).*



Curve A, weight loss (arbitrary ordinate).
B, " Incidence " of water-line attack.
C, " Probability " of water-line attack
D, " Probability " of attack elsewhere.

containing 225 ml. of solution of the composition stated above. Each specimen was suspended from a horizontal glass rod supported by a cork buoy which floated on the surface of the solution, as shown in Fig. 2. The buoys were coated with paraffin wax (previously purified by

boiling with distilled water) to prevent the cork from absorbing water and sinking slightly during the experiment.

After 2 weeks, 8 specimens had suffered attack at the water-line. The average incidence (for 10 specimens) was 0·6. These results are not substantially different from those obtained in earlier experiments. Water-line attack cannot be attributed to slow evaporation.

(4) *Effect of composition of the solution.* Experiments were carried out on specimens immersed to a depth of 2·9 cm. for 168 hours. All solutions contained 0·017M-sodium chloride and varying quantities of an inhibitor (sodium hydroxide, sodium carbonate, disodium hydrogen phosphate, or potassium chromate). Figs. 3—6 show the variation of weight loss with composition; each point is the mean of ten experiments, the vertical lines indicating the scatter.

FIG. 9. *Water-line attack in* Na_2HPO_4–NaCl *solutions (designation of curves as in Fig. 7).*

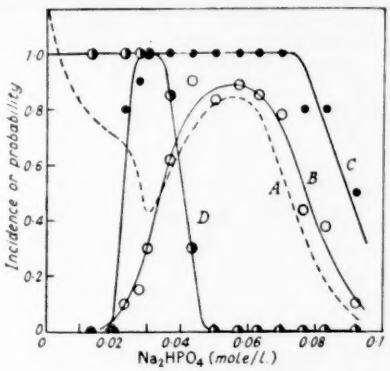


FIG. 10. *Water-line attack in* K_2CrO_4–NaCl *solutions (designation of curves as in Fig. 7).*

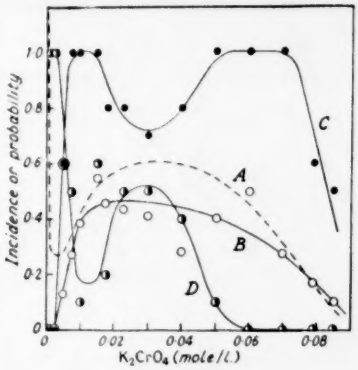


FIG. 11. *Dependence of weight loss on immersed length in* (1) NaCl *solution,* (2) NaCl–Na_2HPO_4 *solution.*

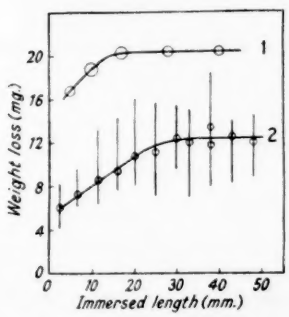
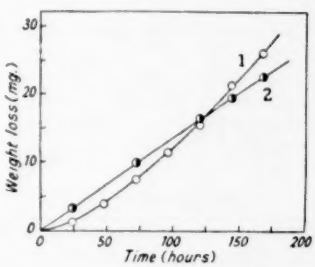


FIG. 12. *Dependence of weight loss on time in* (1) NaCl–Na_2CO_3 *solution,* (2) NaCl *solution.*



In Figs. 7—10, curve *A* shows weight loss (arbitrary ordinates), curve *B* incidence, curve *C* probability of water-line attack, and curve *D* probability of other attack.

Visible corrosion products generally appeared within 1—2 hours and, in almost all cases, were observed first at the meniscus head. At inhibitor concentrations just to the left of the weight-loss minima, before the incidence of water-line attack became appreciable, a neat double line of interference colours was often observed in the meniscus zone, indicating the growth of a visible film which was thickest along a horizontal line through the centre of the meniscus zone and tapered off towards the meniscus head and towards the meniscus foot.

(5) *Vertical dimensions of the specimen.* A large number of specimens were prepared as usual, except that the lengths were varied from 2·2 to 7·0 cm. The specimens were suspended vertically (as in Fig. 1) in 60-ml. beakers containing 41·5 ± 0·5 ml. of solution. The solution contained 0·017M-sodium chloride and 0·045M-disodium hydrogen phosphate. The length of the immersed section was measured from the meniscus head. The experiments were conducted under water-sealed bell jars for 7 days.

In Fig. 11, the average weight loss is plotted against the " immersed length," the distance between the meniscus head and the bottom of the specimen. On curve 2 each point represents the average weight loss for a set of ten specimens of a given length, the vertical line indicating the scatter. Curve 1 was obtained with 0·017M-sodium chloride solution containing no inhibitor. Each point on curve 1 represents the average of 5 specimens, the scatter being here shown by the diameter of the circles. The first point on curve 2 was obtained by adjusting the volume of the solution (within the limits 41·5 ± 0·5 ml.) until the surface of the liquid just touched the lower edge of the specimen; the recorded value (2·5 mm.) is the height of the meniscus.

(6) *Effect of time of immersion.* Seventy specimens were cleaned and vertically suspended in 60-ml. beakers containing 30 ml. of carbonate–chloride solution. The composition of the solution corresponded to the maximum weight-loss of Fig. 4 (0·017M-NaCl + 0·067M-Na_2CO_3). 25 Specimens were suspended under identical conditions in 0·017M-sodium chloride containing no inhibitor.

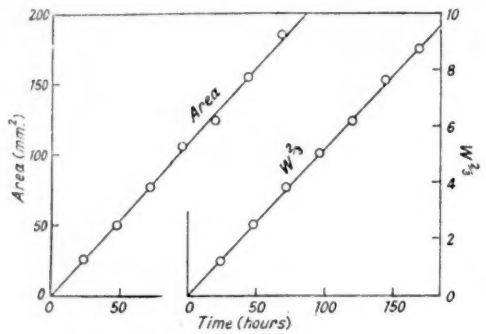


FIG. 13. *Linear dependence of area etched and (weight loss)$^{\frac{1}{2}}$ on time in* NaCl–Na_2CO_3 *solution.*

FIG. 14. *Device for controlling angle of inclination of the specimen.*

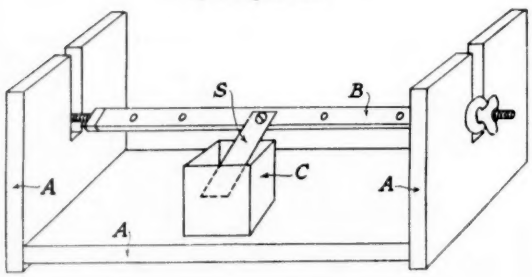
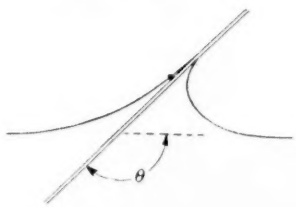


FIG. 15. *Schematic representation of dependence of dimensions of meniscus " crevice " on angle of inclination, θ.*



Each point on curve 1, Fig. 12, represents the average weight-loss for a set of 10 specimens in carbonate–chloride, and each point on curve 2 the average of 5 specimens in the chloride free from inhibitor. Curve 2 is rectilinear, in agreement with Evans and Hoar's results (*Proc. Roy. Soc.*, 1932, *A*, **137**, 343). In the carbonate–chloride solution, the variation in weight loss (W) with time (t) obeys the empirical equation $W = kt^{\frac{1}{2}}$, where k is a constant, as shown by Fig. 13.

The corroded area on each specimen, measured to within about ±1 mm.² by means of transparent graph paper, was found to increase linearly with time, as shown in Fig. 13; each point represents an average for 10 specimens.

(7) *Effect of shape of crevice.* Ten specimens were coated to within 3 cm. of the lower edge with a solution of paraffin wax in xylene. The film of paraffin, when dry, was thin enough to exhibit interference colours. The specimens were suspended vertically (as in Fig. 1) in 60-ml. beakers. 30 ± 1 Ml. of solution containing 0·017M-NaCl and 0·0435M-Na_2HPO_4 were added to each beaker until the meniscus was abolished by meeting the lower edge of the paraffin film (the liquid–solid contact angle now slightly exceeded 90°). Except for traces of corrosion product at the cut edges of two specimens, no visible attack was observed at the water-line in 7 days. Evidently, suppression of the meniscus crevice suppresses water-line attack.

Another arrangement (Fig. 14) permitted gradual variation of the angle. The frame *A*, was of thick aluminium sheet. The movable beam *B*, of insulating material, carried five holes and could be rotated to any desired position. The specimen *S* (2 × 7 cm.) was fixed to the beam by means of brass nuts and bolts. The solution was contained in a square vessel *C*, measuring approximately 4 × 4 × 4 cm., each containing 55 ml. of phosphate–chloride solution of the composition 0·017M-NaCl and 0·075M-Na_2HPO_4, which was chosen as representing a range where both the probability and incidence of attack at the water-line changed rapidly with the inhibitor-concentration (see Fig. 9). The length of the immersed section was set at 24 ± 2 mm. by vertical adjustment of the beam. Only one face of each specimen was exposed to the solution, the other being " masked " by application of polystyrene solution in xylene followed by paraffin wax.

Fig. 15 shows the relation between the angle of inclination of the specimen and the dimensions of the meniscus crevice, which becomes narrower as θ becomes smaller.

FIG. 16. *Arrangement of glass rods (A and B) for observing crevice corrosion.*

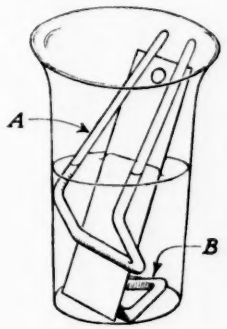
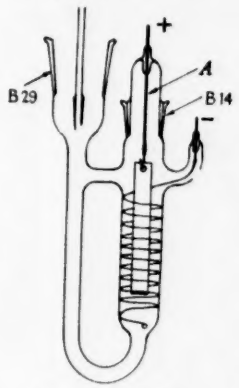


FIG. 17. *Cell B1, for observing distribution of anodic attack in oxygen-free solutions.*



The incidence and probability of attack at the water-line, after 7 days, are recorded in the following table: θ is the angle between the (exposed) surface of the specimen and the horizontal, measured through the liquid phase. Each value represents the average of 15 specimens.

Angle θ	30° *	60° *	90°	120° †	150° †
Incidence	0·71	0·52	0·35	0·27	0·26
Probability	0·73	0·53	0·40	0·30	0·30

* Upper face exposed. † Lower face exposed.

One early set of experiments gave different results. Square drops were obtained by placing liquid (0·017M-NaCl and 0·0435M-Na_2HPO_4) on a " chessboard " of waxed lines (Mears and Evans, *Trans. Faraday Soc.*, 1935, **31**, 527); by adjusting the volume of liquid applied to a square of fixed area, the apparent marginal angle could be controlled between wide limits. No significant variation of probability with angle was observed. The discrepancy is explained later.

The crevice corrosion obtained with glass rods (*A* and *B*, Fig. 16) was compared with water-line corrosion obtained as usual, 30 specimens being used. Observations supported the idea that the same mechanism is responsible for both phenomena.

Series II.—Method. The distribution of attack on mild-steel anodes partly immersed in oxygen-free solutions was observed after passage of a current of 12—13 μamp. on an immersed area 4 × 0·8 cm.(each side) for times varying from 13·6 to 120 hours. The anodes, measuring 0·8 × 6·0 cm., were individually annealed *in vacuo* for 1 hour at 950°. Where films of interference-tint thickness were desired, the annealed anodes were reduced in hydrogen at 750° and then exposed to purified oxygen at 225°. The procedure for annealing, reduction, and oxidation was similar to that of Gulbransen (*Trans. Electrochem. Soc.*, 1942, **81**, 327).

The Pyrex cell, *B*1 (Fig. 17) 1·8 cm. in diameter, was attached by a B 29 ground joint to the apparatus shown in Fig. 18 (in place of cell *B*). The anode was suspended from a hook of thick

platinum wire attached with silver solder to the tungsten rod, *A*, which was sealed through the top of the B 14 joint. The electrical connection to the cathode also involved a vacuum-tight tungsten–Pyrex seal. The cathode was a platinum spiral which fitted snugly against the inner wall of the cell.

The solution (15 ml.) was freed from (and analysed for) oxygen in cell *A* (Fig. 18) by a method described by Peers (*Chem. and Ind.*, 1952, 969) and then transferred into cell B1 through the siphon tube, *C*. The small constant current was obtained from a 120-volt dry battery in series with a large resistance.

Results. In dilute sodium chloride containing no inhibitor apart from the alkali produced at the cathode (which caused the pH to rise from 6·5 to 9·5 where it remained stationary, the solubility product of ferrous hydroxide having been reached), the attack was general, provided the specimen carried only the film normally present after exposure to cold air. On tinted specimens, attack became increasingly *localized* at the meniscus as the film became thicker; for a given film thickness, the attack became less localized as the sodium chloride concentration was increased (Fig. 19). Specimens carrying only the low-temperature films suffered attack

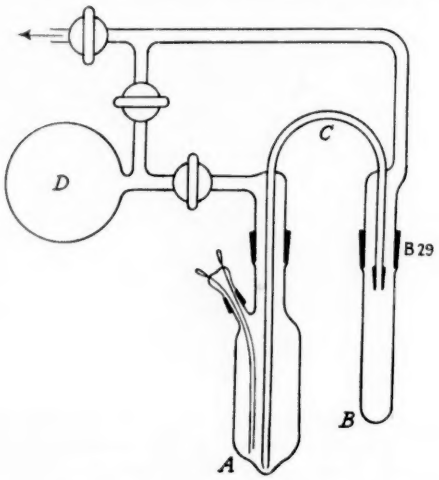


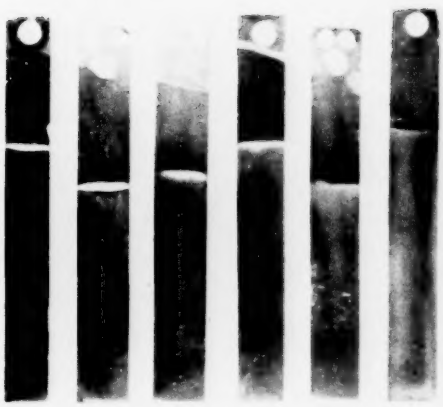
FIG. 18. *See text for explanation. Arrow leads to traps, gauges, gas purification trains, pumps, etc.*

localized at the meniscus if phosphate was present. Thus water-line attack does not need the presence of oxygen.

DISCUSSION

Effect of Films.—The fact that carefully degreased specimens behave much like those not degreased shows that water-line attack is not due to removal of a protective grease film by cathodically produced alkali. A comparison between results obtained in closed and in open vessels, respectively, shows that it is not due to atmospheric acids causing passivity to breakdown locally. The experiments with external current in absence of oxygen show that oxygen is not needed, but that films are important. A specimen which has received no intentional oxidation suffers general attack in sodium chloride free from phosphate and oxygen; but if the specimen is superficially oxidized by heat-tinting, attack is largely confined to the water-line. If the liquid contains sodium phosphate, untinted specimens suffer attack confined to the water-line. Hence either a ready-formed film *or* a film-forming compound is necessary for water-line corrosion.

Corrosion of a film-covered specimen involves either (*a*) the outward movement of electrons through the (dry) oxide-lattice or (*b*) electrolytic migration through sub-microscopic pores which have become filled with liquid. Cationic movement through a lattice will be very slow at room temperature and is likely to be confined to weak spots (Hoar and Evans, *J. Electrochem. Soc.*, 1952, **99**, 212); these may be spots where discontinuities have recently occurred and have been incompletely healed, so that the film has not attained its full thickness. Electrolytic migration will also be limited by the



0·001 0·02 0·05 0·10 0·20 0·50

FIG. 19. *Dependence of distribution of anodic attack on chloride concentration. Anodes had been oxidized for* **20** *min. at* **225°** *under* **12** *cm. of oxygen. Concn. of* NaCl *solution (moles/l.) is given beneath each anode.*

[*To face p.* 1100.

small combined cross-section of the pores. Thus the resistance to *cationic movement* imposed by the film is likely to be large—even though the film conducts electrons well. If we trace the current path between a small area on the metal situated within the crevice and a large cathodic area situated outside it (which may be part of the same specimen, as in natural corrosion, or may be an external platinum wire, as in the anodic experiments), the resistance of the part of the path where it crosses the solid film will be great compared to that of the part in the liquid filling the crevice. In other words, the resistance of a path approaching a small area situated within the crevice will not be appreciably higher than that of a path approaching a similar area outside the crevice; the current density (in absence of inhibitor) would be almost as great within the crevice as outside it, and the inhibitor requirements (for prevention of corrosion) will be almost the same at both places.

If the inhibitor could stop attack only by penetrating the film and reaching the metal, the crevice would have little effect on the replenishment rate compared with the hindrance imposed by the film. However, it seems likely that if inhibitor can reach the *outside* of the film in adequate quantity, it will serve to interact with cations which would otherwise emerge (whether through pores or through the lattice) and prevent them from entering the liquid. Mayne and Menter (unpublished work) find by electron diffraction that the film formed on iron immersed in sodium phosphate is largely γ-ferric oxide with considerable hydrated ferric oxide; the hydration and high oxidation-state suggest formation at the outside of the film. If so, the narrow path approaching a microscopic area within a crevice will impose a greater resistance to diffusion than the broad path approaching a similar area situated outside.

Thus, on a film-covered specimen, the inhibitor-requirements for points situated within a crevice are the same as for points situated outside, whereas the rate of replenishment of inhibitor is much lower within the crevice and the danger of attack there is much greater. This explains the setting up of attack at crevices (including meniscus-crevices), and the argument is equally correct whether the cathode is a platinum wire with externally applied E.M.F. or an area on the specimen itself which can be reached by dissolved oxygen. Hence, in presence of a film the objections to the " exhaustion " theory disappear. The general similarity established between corrosion at the meniscus and that at crevices formed by a glass rod, supports Schikorr's view that the same explanation applies to both.

Effect of Specimen Shape, Time of Immersion, and Liquid Composition.—The uncorroded area is greater on specimens partly immersed in chloride–phosphate (or chloride–carbonate) than in simple chloride solution. If the whole uncorroded area can act as cathode, and if the control is even partly cathodic, the *total* corrosion may be expected to be greater when inhibitor is present; Figs. 3 and 4 show this to be the case. Since the attack is concentrated on a narrow strip along the water-line, the *intensity* is *much* greater. The idea that control is partly cathodic accords with the increase in total corrosion when the immersed length of the specimen is increased (Fig. 11). In simple chloride solution, increase of this dimension (which would mainly increase the anodic area) has less effect on the rate of attack (cf. Evans, *J.*, 1929, 122; Series *A*).

The assumption that the whole uncorroded area acts as cathode may seem to conflict with observations on phosphate-free potassium chloride, where the cathodic reaction was found to be confined to the meniscus zone; in this case, however, there was found to be no oxygen available for the cathodic reaction except at the water-line (Evans and Hoar, *Proc. Roy. Soc.*, 1932, *A*, **137**, 358).

However, the control cannot be wholly cathodic, since the corrosion-rate increases with time (Fig. 12), possibly owing to extension of the anodic area along the water-line in the manner described by Thornhill (*loc. cit.*). Whilst the anodic area is small compared with the cathodic area, a modicum of anodic control must be expected. When the anodic area has ceased to extend laterally (and, to some extent upwards), the velocity is not likely to increase further. Experiments in chloride–phosphate mixtures, lasting 64 days (Evans and Taylor, unpublished work), although showing poor reproducibility, give results suggesting a fairly constant velocity.

An unexpected feature of the curves is the wide range of inhibitor concentration over which water-line attack occurs.

Effect of Crevice Shape.—If water-line corrosion is a form of crevice corrosion, any geometrical alteration which broadens or narrows the crevice should diminish or increase the probability of water-line attack. The experiments with specimens waxed down to the water-line, so as to eliminate the meniscus crevice, showed no water-line attack—which accords with the argument. Those in which the angle was varied by tilting the specimens showed that probability increases as the crevice narrows—which also supports the theory. The square-drop experiments provided an apparent exception, since a reduction of the liquid volume in each drop—although narrowing the contact angle as viewed macroscopically—did not appreciably increase probability. These experiments were carried out before the curves of Fig. 9 were available, and unfortunately a composition was chosen corresponding to the centre of the probability-plateau; thus even though the alteration in the drop shape considerably affected the inhibitor supply, that would be unlikely to affect the probability of water-line attack. The square-drop method was not used again, being unsatisfactory in other ways for the purpose in question; the macroscopic angle may not represent the true angle and the wax may produce micro-crevices if depressions on the metal are bridged but not filled.

General Conclusion.—It appears that water-line corrosion and crevice corrosion are the same phenomenon, and that the attack is due to the inhibitor's being replenished more slowly in crevices than elsewhere, whilst the inhibitor requirements (for prevention of corrosion) are much the same as elsewhere, provided that a film or a film-forming substance is present. Schikorr's views receive general support, and the difficulties in accepting them—valid if films are absent—disappear when films are present. Slow replenishment of the inhibitor anion appears to be the most important factor causing crevice or water-line attack in solutions containing high concentrations of an anodic inhibitor. Nevertheless, the water-line attack produced on mild-steel anodes in mildly alkaline chloride solutions (pH 9·5), suggests that in certain circumstances the local increase in chloride concentration may be as important a cause of localized attack as the decrease in inhibitor anion concentration. One of us (A. M. P.) hopes later to discuss this in detail.

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Department of Metallurgy, Cambridge. [*Received, November 15th*, 1952.]

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223. *The Constitution of Conessine. Part IV.* The Position of the Double Bond and Dimethylamino-group.*

By R. D. Haworth, J. McKenna, and G. H. Whitfield.

Pregna-3 : 5 : 20-triene has been synthesised and found to be identical with the unsaturated hydrocarbon, $C_{21}H_{30}$, obtained by Emde reduction of *apo*-conessine methochloride. The physical data and the degradation of conessine to 3β-dimethylaminopregn-5-ene indicate the positions of the double bond and dimethylamino-group in the alkaloid.

In Part III * the pregnatriene, $C_{21}H_{30}$, m. p. 74—76°, first isolated by Späth and Hromatka (*Ber.*, 1930, **63**, 126) by Emde degradation of *apo*conessine, was shown to yield a mixture of pregnane and *allo*pregnane on catalytic hydrogenation, and it was suggested that the conjugated double bond system of the unsaturated hydrocarbon was in the 3 : 5-position. This conjugated system is formed during Hofmann decomposition of conessine, and is derived from the original double bond of the alkaloid and that formed by the elimination of the dimethylamino-group (Part II, *J.*, 1949, 3127); the isolated double bond of *apo*-conessine and the derived pregnatriene results from the opening of the heterocyclic ring. Analogy with the other steroidal alkaloids suggested that the methylimino-group of the heterocyclic ring in conessine would probably involve the two-carbon side chain at $C_{(17)}$, so that *apo*conessine should have (*a*) a double bond at the 17 : 20-position, (*b*) a double

* Part III, *J.*, 1951, 1736.

bond at the 20 : 21-position, or (*c*) a dimethylamino-group at $C_{(20)}$ or $C_{(21)}$. Of these possibilities, (*a*) appeared to be excluded by the generalised Hofmann rule (formation of the least substituted ethylene), and (*c*) by the fact that neither *apo*conessine nor its hexahydro-derivative can be degraded to a hydrocarbon by further Hofmann decomposition (Späth and Hromatka, *loc. cit.*; Part II, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115). No structural, polar, or stereochemical influences could be envisaged which would completely prevent the elimination of trimethylamine from a $C_{(20)}$- or $C_{(21)}$-trimethylammonium hydroxide, and indeed Julian, Meyer, and Printy (*J. Amer. Chem. Soc.*, 1948, **70**, 887) have recorded two examples of ready Hofmann decomposition of $C_{(20)}$-amines. It seemed possible, therefore, that the isolated double bond in *apo*conessine and the derived pregnatriene, m. p. 74—76°, was at the 20 : 21-position, and the synthesis of pregna-3 : 5 : 20-triene (I) was accordingly undertaken (as already briefly recorded: Haworth and McKenna, *Chem. and Ind.*, 1951, 312).

The preparation of 3β-hydroxypregna-5 : 20-diene and the corresponding toluene-*p*-sulphonate has been described by Julian, Meyer, and Printy (*loc. cit.*), and we are greatly indebted to Dr. Julian for a generous sample of 3β-acetoxy-20-dimethylaminopregn-5-ene from which these two compounds were obtained. Dehydration of the hydroxy-diene by heating it with anhydrous copper sulphate, or treatment of the toluene-*p*-sulphonyl ester with boiling dimethylaniline gave a hydrocarbon $C_{21}H_{30}$, m. p. 74—76°, identical with the pregnatriene obtained from *apo*conessine. This hydrocarbon is formulated as (I) because of the analogous dehydration of cholesterol to cholesta-3 : 5-diene (Mauthner and Suida, *Monatsh.*, 1896, **17**, 29) and of the characteristic ultra-violet absorption ($\lambda_{max.}$, in ethanol, 2350 Å; $\log \varepsilon = 4{\cdot}4$) and high lævorotation.

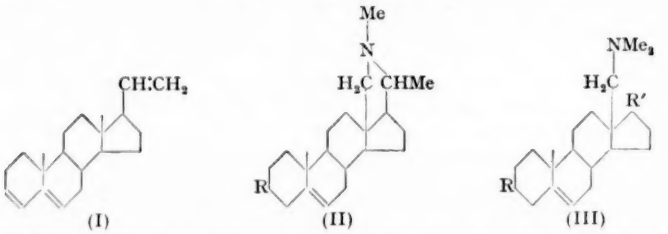
The structure of Späth and Hromatka's pregnatriene being thus demonstrated, two important conclusions (which had been anticipated earlier) followed: first, that the conessine heterocyclic methylimino-group does indeed involve $C_{(20)}$ or $C_{(21)}$ and some other carbon atom in the neighbourhood; and, secondly, that the double bond and the dimethylamino-group of the alkaloid are situated in the neighbourhood of $C_{(5)}$. Preliminary attempts to identify the position of the conessine double bond were made by a study of the base dioxyconessine (more correctly dihydroxydihydroconessine), $C_{24}H_{42}O_2N_2$, produced by oxidation of conessine with potassium iodate (Warnecke, *Arch. Pharm.*, 1888, **226**, 248). A Zerewitinoff determination showed the presence of two active hydrogen atoms, and the simplest formulation for the base would be an α-glycol formed by hydroxylation of the conessine double bond; a solution of dioxyconessine in dilute sulphuric acid was unattacked, however, by periodic acid at room temperature. Oxidation of 3β-dimethylaminocholest-5-ene (Dodgson and Haworth, *J.*, 1952, 67) with potassium iodate gave a similar high-melting base, $C_{29}H_{53}O_2N$, which is regarded as 3β-dimethylamino-5ξ : 6ξ-dihydroxycholestane. Like dioxyconessine, this base contained two active hydrogen atoms.

Dioxyconessine is more soluble in water than conessine, and it was at first thought that it was a ψ-base, similar to berberine or cotarnine (for a recent discussion, see Skinner, *J.*, 1950, 823). Potentiometric titration of an aqueous solution of dioxyconessine dihydrochloride with standard alkali showed, however, that the basic strength is of the same order as that of ammonia; and no sensible differences in the titration curves were observed when the dihydrochlorides of conessine and dioxyconessine were titrated against standard alkali in 20% aqueous acetone or absolute methanol. The titration curve for 3β-dimethylamino-5ξ : 6ξ-dihydroxycholestane in 20% aqueous acetone indicates that this base is weaker than dioxyconessine, probably because it lacks the second basic centre of the alkaloid derivative.

In a more systematic effort to identify the positions of the dimethylamino-group and the double bond, conessine was submitted to a series of degradation reactions, the ultimate aim of which was to eliminate the methylimino-group without disturbing the position of the other two functions. Formula (II; $R = NMe_2$) has been proposed for conessine (Haworth, McKenna, Powell, and Whitfield, *Chem. and Ind.*, 1952, 215) and is now employed for illustrating the degradation reactions; more detailed arguments in favour of

this formula are developed in this paper (for rings A and B) and in Part VI (*J.*, 1953, 1115, for the heterocyclic structure).

Degradation of conessine with cyanogen bromide according to Siddiqui and Siddiqui's method (*J. Indian Chem. Soc.*, 1934, **11**, 787) gave *iso*conessimine (II; R = NHMe); the



(I) (II) (III)

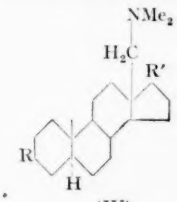
formulation $NHMe{\cdot}C_{21}H_{31}{>}NMe$, proposed without proof by these authors for this base (which also occurs in Nature associated with conessine) is confirmed by our work. Thus the demethylation of conessine to *iso*conessimine, and the methylation of the latter to conessine (*idem ibid.*), indicate that *iso*conessimine must have one of the formulations $NHMe{\cdot}C_{21}H_{31}{>}NMe$ or $NMe_2{\cdot}C_{21}H_{31}{>}NH$; if, however, the latter were correct, the Hofmann degradation of *N*-acetyl*iso*conessimine described below should give a non-basic compound containing only one nitrogen atom.

N-Acetyl*iso*conessine (II; R = NMeAc) was converted into its methiodide, and this salt submitted to Hofmann degradation in the usual manner. The product was a dinitrogenous monoacid base, *N*-acetyl*iso*conessimine methine (III; R = NMeAc, R′ = $CH{:}CH_2$). Pyrolysis of the methohydroxide derived from this base did not result in further Hofmann degradation. *N*-Acetyl*iso*conessimine methine was cyclised to a quaternary methoacetate on being refluxed in acetic acid solution. This behaviour is typical of that of methine bases in the conessine series (Part III, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115) and serves to indicate, together with the relations established (see below) with conessimethine and tetrahydroconessimethine, that during the Hofmann reaction of *N*-acetyl*iso*conessimine, the heterocyclic ring has opened in the usual way, leaving a dimethylamino-group in the *apo*conessine position, and a double bond at position 20 : 21. Partial hydrogenation of the acetyl-methine in alcohol gave *N*-acetyl-20 : 21-dihydro*iso*conessimine methine (III; R = NMeAc, R′ = Et), so formulated because it was not cyclised in boiling acetic acid. Hydrogenation of this base in glacial acetic acid gave the fully saturated *N*-acetyltetrahydro*iso*conessimine methine (IV; R = NMeAc, R′ = Et).

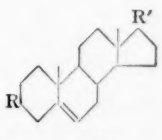
At this point a detour was made from the main degradation scheme in order to relate *N*-acetyl*iso*conessimine methine to other methine bases in the conessine series. Alkaline hydrolysis of the acetyl methine (III; R = NMeAc, R′ = $CH{:}CH_2$) gave *iso*conessimine methine (III; R = NHMe, R′ = $CH{:}CH_2$); on methylation with formaldehyde and formic acid this gave the base conessimethine (III; R = NMe_2, R′ = $CH{:}CH_2$), m. p. 77—78°, which had shortly before been isolated from the reaction mixture obtained by partial Hofmann decomposition of conessine (*idem, ibid.*, p. 1127). Conessimethine gave a little impure *apo*conessine on Hofmann degradation. Hydrolysis of *N*-acetyltetrahydro*iso*conessimine methine with concentrated hydrochloric acid gave tetrahydro*iso*conessimine methine (IV; R = NHMe, R′ = Et), which was methylated with formaldehyde and formic acid to tetrahydroconessimethine (IV; R = NMe_2, R′ = Et). This base may also be obtained by reduction of conessimethine or of the methine base, $C_{25}H_{46}N_2$, m. p. 66—70°, from dihydroconessine (Haworth, McKenna, and Whitfield, *loc. cit.*; Part III, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1126). It was evident, therefore, that Hofmann decomposition of *N*-acetyl*iso*conessimine had resulted in a fission of the heterocyclic ring in the usual way, thus justifying the placing of a double bond at position 20 : 21 in the derived methine.

In continuation of the main degradation scheme, Emde reduction of *N*-acetyl*iso*conessimine methine methochloride gave an *N*-acetyl-*N*-methylaminopregnadiene (V;

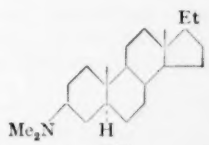
R = NMeAc, R′ = $CH{:}CH_2$), m. p. 184—185°, yielding an *N*-acetyl-*N*-methylaminopregnene (V; R = NMeAc, R′ = Et) on partial hydrogenation in alcohol. Hydrolysis of this pregnene with alcoholic potash gave a methylaminopregnene (V; R = NHMe, R′ = Et); this base on methylation with formaldehyde and formic acid gave a dimethylaminopregnene (V; R = NMe_2, R′ = Et), m. p. 119°, which on hydrogenation gave the saturated tertiary base, m. p. 95—96°. The course of the above series of reactions indicated that the *N*-acetyl-*N*-methylaminopregnadiene, m. p. 184—185°, had an acetylmethylamino-group corresponding in position to the conessine dimethylamino-group, a double bond corresponding in position to the original conessine double bond, and a 20 : 21-double bond. By analogy with the result of partial hydrogenation of *N*-acetyl*iso*conessimine methine (see above) it was argued that the 20 : 21-double bond underwent preferential hydrogenation at the next stage in the reaction scheme, so that the dimethylaminopregnene, m. p. 119°, and the saturated base, m. p. 96°, should correspond respectively to conessine and dihydroconessine.



(IV)



(V)



(VI)

At this stage an evaluation was made of the available physical evidence relating to the position of the double bond in conessine and in the corresponding dimethylaminopregnene, m. p. 119°.

(a) *Infra-red absorption.* The infra-red absorption curves of conessine and the dimethylaminopregnene, m. p. 119°, show maxima at 798, 826, 1665 cm.$^{-1}$ and 797, 829, and 1660 cm.$^{-1}$, respectively. The curve for 3β-dimethylaminocholest-5-ene shows maxima at 796, 827, and 1660 cm.$^{-1}$. These results indicate that conessine and the dimethylaminopregnene, m. p. 119°, have the double bond situated at either the 5 : 6- or the 7 : 8-position (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402); it is not possible to differentiate these two positions by this method, but other trisubstituted positions such as the 4 : 5 and all disubstituted positions are excluded.

(b) *Ultra-violet absorption.* A valuable new spectroscopic method for determining the degree of substitution and sometimes the actual position of an isolated double bond in the steroid nucleus by measurement of the " end absorption " has recently been introduced by Bladon, Henbest, and Wood (*J.*, 1952, 2737). Application of this method showed that the absorption curves (see Fig.) of the dimethylaminopregnene, m. p. 119°, and 3β-dimethylaminocholest-5-ene were practically superimposed in both neutral and acidic ethanol solution, and that either curve in neutral ethanol is very nearly identical with that given by cholest-5-ene. Although the hydrocarbons cholest-4- and -5-ene can hardly be distinguished by this method, it seems likely that the close agreement established between the two unsaturated *bases* is very significant, as one might well expect a different curve with a 3-dimethylamino-$\Delta^{4:5}$-steroid on account of the proximity of the basic centre to the double bond (compare Bladon, Henbest, and Wood's discussion, *loc. cit.*). It is rather surprising, in fact, that the absorption curves for cholest-5-ene and 3β-dimethylaminocholest-5-ene are so similar. The absorption curves for conessine, in neutral and acidic ethanol (see Fig.), are quite different from those given by the monoacid bases, and at first gave rise to errors in interpretation, but it now seems evident that the methylimino-group alters the absorption due to the double bond so much that nothing can be deduced by this method from a study of the alkaloid itself.

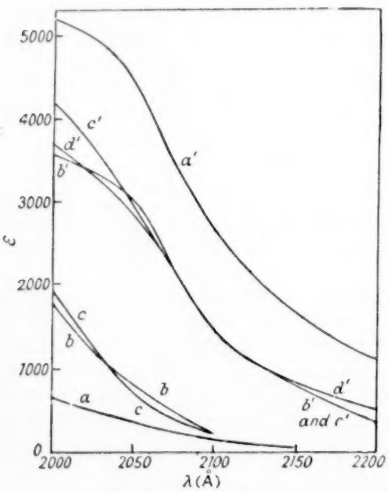
(c) *Optical-rotation studies.* Molecular-rotation data favour a 5 : 6-double bond for conessine and the derived dimethylaminopregnene. A detailed discussion is given in Part VI (*J.*, 1953, 1115).

Taken as a whole, therefore, the physical data and the properties of dioxyconessine suggested that the conessine double bond was at position 5 : 6, and the ultra-violet absorption evidence favoured a 3β-dimethylamino-group. These conclusions were confirmed by complementary synthetical work described in Part V (following paper) by which the acetylmethylaminopregnadiene, m. p. 184—185°, and the saturated tertiary base, m. p. 96°, obtained from conessine have been identified with synthetic specimens of 3β-acetylmethylaminopregna-5 : 20-diene (V; R = NMeAc, R′ = CH:CH_2) and 3β-dimethylamino*allo*pregnane (VI) respectively. The position of attachment of the heterocyclic methylimino-group is considered in Part VI (*J.*, 1953, 1115).

Experimental

Optical rotatory values given in this and the two following papers were determined at room temperature (15—25°).

Pregna-3 : 5 : 20-triene (I).—(*a*) A mixture of 3β-hydroxypregna-5 : 20-diene (Julian, Meyer, and Printy, *loc. cit.*) (500 mg.) and anhydrous copper sulphate (10 g.) was distilled at 0·01 mm.



In acidic ethanol	In ethanol	
a	*a′*	Conessine.
b	*b′*	3β-Dimethylaminocholest-5-ene.
c	*c′*	3β-Dimethylaminopregn-5-ene.
	d′	Cholest-5-ene.

(bath temp. 200°), and the distillate (200 mg.) recrystallised several times from methanol, yielding the hydrocarbon as colourless, prismatic needles, $[\alpha]_D$ −210° (in $CHCl_3$, *c* 0·3), m. p. 74—76° (Found: C, 88·8; H, 10·8. Calc. for $C_{21}H_{30}$: C, 89·3; H, 10·7%), undepressed on admixture with the hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, $[\alpha]_D$ −210° (in $CHCl_3$, *c* 0·3), obtained from conessine.

(*b*) A solution of pregna-5 : 20-dien-3β-yl toluene-*p*-sulphonate (Julian, Meyer, and Printy, *loc. cit.*) (70 mg.) in dry dimethylaniline (1 c.c.) was refluxed for 20 minutes, cooled, treated with excess of dilute hydrochloric acid, and extracted with ether. The extract was washed with hydrochloric acid and water, and evaporated; the partly crystalline residue (35 mg.), which could not be purified by chromatography, was distilled at 0·005 mm. (bath temp. 100°), and the distillate (20 mg.) crystallised several times from methanol, giving colourless prismatic needles, $[\alpha]_D$ −200° (in $CHCl_3$, *c* 0·07), m. p. 74—76°, undepressed on admixture with the hydrocarbon, $C_{21}H_{30}$, obtained from conessine.

3β-*Dimethylamino*-5ξ : 6ξ-*dihydroxycholestane*.—A solution of the 3β-dimethylaminocholest-5-ene (V; R = NMe_2, R′ = C_8H_{17}) (0·6 g.) (Dodgson and Haworth, *loc. cit.*) in glacial acetic acid (10 c.c.) was treated with potassium iodate (0·6 g.) in 2N-sulphuric acid (10 c.c.), and the mixture boiled for 15 minutes, evolution of iodine then having ceased. The solution was cooled, made alkaline with ammonia, and extracted five times with ether. Evaporation of the extracts and crystallisation of the residue from ethanol gave the dihydroxy-*base* as colourless, rectangular needles (0·41 g.), m. p. 208—209° (Found: C, 77·4; H, 12·0; N, 3·2. $C_{29}H_{53}O_2N$ requires C, 77·8; H, 11·9; N, 3·1%). The compound evolved 2·1 mols. of methane on treatment with methylmagnesium iodide in anisole at 18°. The *hydrochloride* separated from ether–acetic acid

in needles, m. p. 304—305° (Found: C, 72·5; H, 11·3; N, 3·0. $C_{29}H_{53}O_2N$,HCl requires C, 72·0; H, 11·2; N, 2·9%), almost insoluble in water and ether, and very sparingly soluble in alcohol and acetone.

Dioxyconessine, m. p. 290°, was prepared by oxidising conessine with potassium iodate and dilute sulphuric acid (Warnecke, *loc. cit.*); it immediately evolved 2·05 mols. of methane on treatment with methylmagnesium iodide in boiling anisole.

Attempted Oxidation of Dioxyconessine with Periodic Acid.—Dioxyconessine (0·107 g.) in 2N-sulphuric acid (5 c.c.) and water (10 c.c.) was treated with approx. M/4-periodic acid prepared from sodium paraperiodate and dilute sulphuric acid (5 c.c.); the mixed solution was kept at room temperature and 1-c.c. aliquots were withdrawn from time to time and titrated with 0·1012N-sodium thiosulphate solution. Immediately after the mixing, the titre was 4·55 c.c., and no change in titre was observed over 60 hours (calculated reduction in titre for one α-glycol group, 0·25 c.c.). Dioxyconessine was recovered unchanged.

Potentiometric Titrations.—The apparatus used was a Marconi pH meter with glass and calomel electrodes which were allowed to reach equilibrium with the solvents for 1½ hours before a titration was carried out; the glass electrode was at other times during the period of the experiments kept in a solution of the solvent in which it was next to operate which had been acidified to N/10 with hydrochloric acid. During the titrations nitrogen was passed over the surface of the solution. Standard N/10- and N/20-sodium hydroxide solutions were made up in the presence of an equivalent normality of barium chloride. N/10-Sodium hydroxide in methanol was obtained by dissolving sodium (0·29 g.) in dry methanol (250 c.c.) and adding distilled water (0·25 c.c.).

iso*Conessimine* (II; R = NHMe).—This compound was obtained from conessine by degradation with cyanogen bromide according to Siddiqui and Siddiqui's method (*loc. cit.*). The base separated from aqueous dioxan in fine, colourless needles, m. p. 95—96°; Siddiqui (*J. Indian Chem. Soc.*, 1934, **11**, 283) gives m. p. 92°. The compound, like conessine, gave no precipitate with digitonin when tested under the usual conditions (Bertho, *Annalen*, 1950, **569**, 1, claims to have obtained an adduct of conessine and digitonin, but we have not been able to confirm this with our samples). The *N*-acetyl derivative separated from light petroleum (b. p. 60—80°) as clumps of needles, m. p. 161° (Found: C, 78·4; H, 10·5; N, 7·9. Calc. for $C_{25}H_{40}ON_2$: C, 78·1; H, 10·4; N, 7·3%) (Siddiqui and Siddiqui, *loc. cit.*, give m. p. 127—128°; this may be a solvated form, as in some of our experiments a product, m. p. 133°, was obtained before drying *in vacuo*).

*Dihydro*iso*conessimine.*—*iso*Conessimine (0·34 g.) in glacial acetic acid (10 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (35 mg.) at 20°/728 mm. Hydrogen uptake (32·3 c.c. Calc. for one double bond and the catalyst: 32·7 c.c.) was complete in 25 minutes. After being shaken in a hydrogen atmosphere overnight, the mixture was filtered, the filtrate evaporated, and the residue treated with ammonia and ether; the *base* from the ethereal extract formed colourless needles (0·19 g.), m. p. 97—98°, from aqueous dioxan (Found: C, 80·2; H, 11·5; N, 7·8. $C_{23}H_{40}N_2$ requires C, 80·2; H, 11·6; N, 8·1%). The N-*acetyl* derivative crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 175—176° (Found: C, 78·0; H, 10·6; N, 6·7. $C_{25}H_{42}ON_2$ requires C, 77·7; H, 10·9; N, 7·3%).

Hofmann Degradation of N-*Acetyl*iso*conessimine.*—N-*Acetyl*iso*conessimine methiodide* separated from aqueous methanol in small, colourless needles, m. p. 290° (decomp.) (Found: C, 58·7; H, 8·5; I, 24·0. $C_{25}H_{40}ON_2,CH_3I$ requires C, 59·3; H, 8·2; I, 24·2%). This salt (6·0 g.) in water (250 c.c.) was shaken overnight with excess of silver oxide, the mixture filtered, the filtrate evaporated to dryness, and the residue heated at 200° (bath temp.)/0·05 mm. in a vacuum-sublimation apparatus. Sublimate and residue were combined and extracted with ether. The N-*acetyl*iso*conessimine methine* (III; R = NMeAc, R′ = $CH{\cdot}CH_2$), recovered from the ethereal extract and recrystallised from light petroleum (b. p. 40—60°), formed hard rosettes of colourless needles (3·6 g.), m. p. 121—122° (Found: C, 78·0; H, 10·4; N, 7·3. $C_{26}H_{42}ON_2$ requires C, 78·4; H, 10·6; N, 7·0%).

Cyclisation of N-*Acetyl*iso*conessimine Methine.*—The base (III; R = NMeAc, R′ = $CH{\cdot}CH_2$) (0·11 g.) was refluxed in glacial acetic acid (2 c.c.) for 30 minutes. The solvent was evaporated, and the residue treated with ammonia; the clear solution yielded no basic material on extraction with ether, but addition of potassium iodide gave an immediate heavy white precipitate (0·12 g.) which on recrystallisation from aqueous methanol gave colourless plates of the cyclised *methiodide*, m. p. 298—300° (decomp.) (Found: C, 59·1; H, 7·6; N, 5·2; I, 24·7. $C_{25}H_{40}ON_2.CH_3I$ requires C, 59·5; H, 8·2; N, 5·3; I, 24·2%).

N-*Acetyl*-20: 21-*dihydro*iso*conessimine Methine* (III; R = NMeAc, R′ = Et).—An ethanolic

solution of *N*-acetyl*iso*conessimine methine (0·47 g.) was shaken in hydrogen at 190°/758 mm. in the presence of Adams's platinum oxide catalyst (50 mg.). The rate of uptake of hydrogen decreased abruptly after 30 minutes, when 37·4 c.c. had been absorbed (Calc. for one double bond and the catalyst: 39·9 c.c.). The *N-acetyl-20 : 21-dihydroisoconessimine methine* separated from ether–light petroleum (b. p. 40—60°) as clumps of colourless needles (0·35 g.), m. p. 135—136° (Found: C, 78·0; H, 11·0; N, 7·0. $C_{26}H_{44}ON_2$ requires C, 78·0; H, 10·8; N, 7·1%). The base was unaffected by refluxing its solution in glacial acetic acid for 30 minutes. It was unsaturated to cold acid permanganate, and liberated iodine readily on boiling with potassium iodate and dilute sulphuric acid.

N-Acetyltetrahydroisoconessimine Methine (IV; R = NMeAc, R′ = Et).—The above dihydrobase (0·262 g.) in glacial acetic acid (10 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (27 mg.) at 16°/740 mm. Hydrogen uptake (23·2 c.c. Calc. for one double bond and the catalyst: 21·8 c.c.) was complete in 15 hours. The *methine* was isolated in the usual way and recrystallised from light petroleum (b. p. 60—80°) as colourless needles (0·211 g.), m. p. 157—158° (Found: C, 78·0; H, 11·3; N, 7·3. $C_{26}H_{46}ON_2$ requires C, 77·6; H, 1·4; N, 7·0%).

iso*Conessimine Methine* (III; R = NHMe, R′ = $CH{\cdot}CH_2$).—*N*-Acetyl*iso*conessimine methine (0·278 g.) was hydrolysed with 20% ethanolic potassium hydroxide at 130° for 40 hours. The *product* separated from ethanol in colourless rhombs (0·113 g.), m. p. 113—114° (Found: C, 80·4; H, 11·3; N, 8·2. $C_{24}H_{40}N_2$ requires C, 80·9; H, 11·2; N, 7·9%).

Conessimethine (III; R = NMe_2, R′ = $CH{\cdot}CH_2$).—*iso*Conessimine methine (0·54 g.) was methylated by formic acid (98%; 2·5 c.c.), water (5 c.c.), and formaldehyde (40%; 2·5 c.c.) on the water-bath for 2 hours. The well-cooled solution was basified with dilute sodium hydroxide and extracted with ether, and the base recovered from the ether with dilute hydrochloric acid. This procedure was repeated and the crude *conessimethine* (0·46 g.) was recrystallised from acetone, yielding fine colourless needles (0·42 g.), m. p. 77—78° (Found: C, 81·8; H, 11·1; N, 7·9. $C_{25}H_{42}N_2$ requires C, 81·1; H, 11·3; N, 7·6%) undepressed on admixture with a sample prepared by partial Hofmann degradation of conessine (see Part VI, *J.*, 1953, 1127). Only a small proportion of the unsaturated bases was cyclised during the methylation.

Hofmann Degradation of Conessimethine.—Conessimethine dimethiodide separated from aqueous methanol as colourless prismatic needles, m. p. 320° (decomp.) (Found: N, 4·7. $C_{25}H_{42}N_2,2CH_3I$ requires N, 4·5%). Distillation of the corresponding methohydroxide, prepared in the usual way, at 140° (bath temp.)/0·005 mm., yielded a base which after purification *via* the insoluble sulphate and several recrystallisations gave a somewhat impure sample of *apo*conessine, m. p. 65—67° undepressed on admixture with an authentic specimen, m. p. 68—69°.

Tetrahydroisoconessimine Methine (IV; R = NHMe, R′ = Et).—*N*-Acetyltetrahydro*iso*conessimine methine (IV; R = NMeAc, R′ = Et) was not hydrolysed by refluxing for 20 hours with equal volumes of ethanol and concentrated hydrochloric acid. The acetyl derivative (0·21 g.) was heated at 140° for 40 hours with concentrated hydrochloric acid (5 c.c.). The acid solution was diluted, extracted with ether, and basified, and the base taken up in ether; the ethereal extract was washed and evaporated, leaving a brown oil (0·18 g.), which was treated with light petroleum (b. p. 40—60°) (10 c.c.) and the solution filtered. The base (IV; R = NHMe, R′ = Et) recovered from the filtrate was sublimed at 0·05 mm. (bath temp. 230°) and recrystallised from acetone, separating as colourless needles (80 mg.), m. p. 74° (Found: C, 80·0; H, 12·1; N, 7·9. $C_{24}H_{44}N_2$ requires C, 80·0; H, 12·2; N, 7·8%).

Tetrahydroconessimethine (IV; R = NMe_2, R′ = Et).—Methylation of tetrahydro*iso*conessimine methine (42 mg.) with formic acid (98%; 0·5 c.c.), water (1 c.c.), and formaldehyde (40%; 0·5 c.c.) for 3 hours on the water-bath in the usual way gave *tetrahydroconessimethine* (42 mg.), which on recrystallisation from acetone formed colourless needles (30 mg.), m. p. 83—84°. After vacuum sublimation and further recrystallisation the m. p. was 88—89° (Found: C, 79·4; H, 12·2; N, 7·9. $C_{25}H_{46}N_2$ requires C, 80·2; H, 12·3; N, 7·5%), undepressed on admixture with a sample, m. p. 85—86°, prepared by hydrogenation of dihydroconessine methine (Part III, *loc. cit.*).

Attempted Hofmann Degradation of N-Acetylisoconessimine Methine.—N-Acetylisoconessimine methine methiodide separated from methanol in small, colourless needles, m. p. 247° (decomp.) (Found: N, 5·6; I, 23·9. $C_{26}H_{42}ON_2,CH_3I$ requires N, 5·2; I, 23·5%). The methohydroxide solution from this salt (0·5 g.) was evaporated, and the residue heated at 0·05 mm. (bath temp. 200°). The resulting base (0·285 g.) separated from light petroleum (b. p. 40—60°) in colourless needles, m. p. 110—113°, not raised by repeated recrystallisation, or by chromatography on

alumina. No depression in m. p. was observed on admixture with *N*-acetyl*iso*conessimine methine, m. p. 121—122°.

Emde Reduction of N-Acetylisoconessimine Methine Methochloride.—The foregoing methiodide (0·7 g.) was converted into methochloride by heating its solution in water (25 c.c.) with excess of silver chloride for 12 hours at 100°. The *methochloride* crystallised from methanol–ether as small, colourless needles (0·45 g.), m. p. 207° (decomp.) (Found: N, 6·3; Cl, 8·0. $C_{26}H_{42}ON_2,CH_3Cl$ requires N, 6·2; Cl, 7·9%). A continuous stream of carbon dioxide was passed through a solution of the methochloride (0·2 g.) in water (100 c.c.) at 100° during the addition (12 hours) of 5% sodium amalgam (200 g.). The mixture was cooled and extracted with ether, and the extract washed with water and then with dilute hydrochloric acid; from the acidic washings *N*-acetyl*iso*conessimine methine (40 mg.) was recovered. The residue (72 mg.) from the ethereal solution was recrystallised from ethanol, yielding colourless leaflets of 3β-*acetylmethylaminopregna*-5 : 20-*diene* (V; R = NMeAc, R′ = $CH{\cdot}CH_2$), m. p. 184—185° (Found: C, 80·8; H, 10·1; N, 3·9. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·4; N, 3·9%), undepressed on admixture with an authentic specimen (see Part V, *J.*, 1953, 1113).

3-*Acetylmethylaminopregn*-5-*ene* (V; R = NMeAc, R′ = Et).—A solution of the foregoing compound (0·72 g.) in warm ethanol (50 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (22 mg.). Hydrogen uptake (54 c.c. at 18°/751 mm. Calc. for one double bond and the catalyst: 53·7 c.c.) was complete in 2·5 hours. The *product*, recrystallised from chloroform–light petroleum (b. p. 90—120°), formed colourless needles (0·68 g.), m. p. 206° (Found: C, 80·2; H, 10·6; N, 4·1. $C_{24}H_{39}ON$ requires C, 80·7; H, 10·9; N, 3·9%).

3β-*Methylaminopregn*-5-*ene* (V; R = NHMe, R′ = Et).—The above acetyl derivative (0·6 g.) was hydrolysed by 20% ethanolic potassium hydroxide (15 c.c.) at 140° for 50 hours. The resultant *base* (0·54 g.) crystallised from ethanol as colourless, silky needles, m. p. 134—135° (Found: C, 83·7; H, 11·5; N, 4·5. $C_{22}H_{37}N$ requires C, 83·8; H, 11·7; N, 4·4%).

3β-*Dimethylaminopregn*-5-*ene* (V; R = NMe_2, R′ = Et).—Methylation of (V; R = NHMe, R′ = Et) (0·2 g.) with formic acid (2·5 c.c. of 90%), water (5 c.c.), and formaldehyde (2·5 c.c. of 40%) for 3 hours at 100° and recrystallisation of the product from acetone gave the *dimethylamino*-compound as colourless needles, m. p. 119°, $[\alpha]_D$ −37·5° (in $CHCl_3$, *c* 1·5) (Found: C, 83·3; H, 11·9; N, 4·4. $C_{23}H_{39}N$ requires C, 83·9; H, 11·9; N, 4·3%).

3β-*Dimethylamino*allo*pregnane* (VI).—The above unsaturated base (0·1 g.) in glacial acetic acid (10 c.c.) was hydrogenated overnight in the presence of Adams's platinum oxide catalyst (39 mg.) (Hydrogen uptake, 16·4 c.c. at 20°/757 mm. Calc. for one double bond and the catalyst: 16·1 c.c.). The saturated *base* crystallised from acetone as colourless needles (87 mg.), $[\alpha]_D$ +17·5° (in $CHCl_3$, *c* 2·0), m. p. 96—56° (Found: C, 83·3; H, 12·5; N, 4·0. $C_{23}H_{41}N$ requires C, 83·4; H, 12·4; N, 4·2%) undepressed on admixture with an authentic specimen of 3β-dimethylamino*allo*pregnane (*J.*, 1953, 1112).

Our thanks are offered to the University of Sheffield for the award of a Henry Ellison Fellowship to G. H. Whitfield, and to Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of this investigation. The infra-red and some of the ultraviolet absorption measurements were kindly made for us by Drs. H. B. Henbest and G. D. Meakin and Mr. G. W. Wood in Professor E. R. H. Jones's laboratories at Manchester University.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 17th*, 1952.]

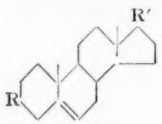
224. *The Constitution of Conessine. Part V.* Synthesis of Some Basic Steroids.*

By R. D. Haworth, J. McKenna, and R. G. Powell.

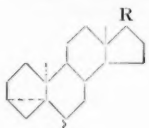
The synthesis is described of a variety of amines related to cholestane and *allo*pregnane. Some of these are identical with conessine degradation products, and the constitution of others has not yet been determined. Significant differences in ease of Hofmann decomposition have been observed with saturated epimeric 3-amines.

The synthesis of some basic derivatives of steroids has been described by Dodgson and Haworth (*J.*, 1952, 67 †), and the present paper records further work in this field, some of which was undertaken in order to provide synthetic samples for comparison with conessine degradation products described in the preceding paper.

3β-Hydroxypregn-5-ene (I; R = OH, R′ = Et) was prepared by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1949, **71**, 3301), and the toluene-*p*-sulphonyl ester (I; R = *p*-O·SO_2·C_6H_4Me, R′ = Et) treated with dimethylamine at 100°. The sole product was a base $C_{23}H_{39}N$, m. p. 130°, which yielded a dihydro-derivative $C_{23}H_{41}N$, m. p. 78—79°, on catalytic hydrogenation. The base did not liberate iodine when its solution in glacial acetic acid was boiled for two minutes with a solution of potassium iodate in 2N-sulphuric acid; under the same conditions conessine and authentic 3β-dimethylaminocholest-5-ene



(I)



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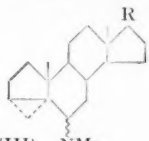


(III)

(Dodgson and Haworth, *loc. cit.*) were readily oxidised. Furthermore, the dihydro-derivative was not identical with 3α- or 3β-dimethylamino*allo*pregnane prepared by the unambiguous syntheses described below. It was evident therefore that the reaction of the toluene-*p*-sulphonyl ester with dimethylamine gave not dimethylaminopregn-5-ene (I; R = NMe_2, R′ = Et) but an isomeric base, $C_{23}H_{39}N$, the structure of which is under investigation. It may have a 3 : 5-*cyclo*-structure such as (II or III; R = Et; cf. Julian, Magnani, Meyer, and Cole, *J. Amer. Chem. Soc.*, 1948, **70**, 1834).

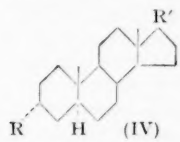
For the preparation of 3α-dimethylamino*allo*pregnane (IV; R = NMe_2, R′ = Et), allopregnan-3β-ol (V; R = OH, R′ = Et) was prepared by Huang-Minlon's method (*loc. cit.*), and the corresponding toluene-*p*-sulphonyl ester (V; R = *p*-O·SO_2·C_6H_4Me, R′ = Et) treated at 100° with dimethylamine. The product is assigned the 3α-configuration, as displacement reactions of 3-toluene-*p*-sulphonates in steroids saturated in rings A and B are known to be accompanied by Walden inversion (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1947, pp. 642, 643). The isomeric 3β-dimethylamino*allo*pregnane was prepared from *allo*pregnan-3-one (Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1947, **30**, 877) by reduction of the oxime with sodium and amyl alcohol and proved to be identical with the base, m. p. 96°, obtained by degradation of conessine as described in the preceding paper. The oxime reduction was expected to yield predominantly the 3β-isomer (equatorial) as in the case of the similar reduction of the oxime of cholestan-3-one (Dodgson and Haworth, *loc. cit.*). The configuration assigned to these basic *allo*pregnanes is confirmed by the results of the Hofmann degradation described below.

* Part IV, preceding paper.

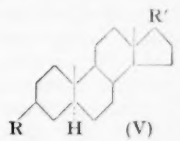
† We draw attention to some errors in this paper:
P. 68, l. 5 (from bottom). *For* "bishydroxyaminoandrostane" *read* "dioximinoandrostane."
P. 69, l. 19. *For* "Hydroxyaminocholestane" *read* "Oximinocholestane."
P. 71, l. 31. *For* "(III)" *read* "(IV)." *For* "Bishydroxyaminoandrostane" *read* "dioximinoandrostane."
l. 38. *For* "(V)" *read* "(IV)."

For the synthesis of 3β-*N*-acetyl-*N*-methylaminopregna-5 : 20-diene (I; R = NMeAc, R′ = CH:CH_2) required for comparison with the acetylmethylaminopregnadiene, m. p. 182—183°, obtained from conessine, the toluene-*p*-sulphonyl ester of 3β-hydroxypregna-5 : 20-diene (I; R = *p*-O·SO_2·C_6H_4Me, R′ = CH:CH_2) was prepared as described by Julian, Meyer, and Printy (*J. Amer. Chem. Soc.*, 1948, **70**, 887) and treated with methylamine at 100° in the usual way. Two isomeric bases, $C_{22}H_{35}N$, were obtained. One of these, which gave a negative iodate reaction, yielded an *N*-acetyl derivative, m. p. 113—114°, and was converted on methylation and catalytic hydrogenation into the base, $C_{23}H_{41}N$, m. p. 78—79°, obtained as described above; this isomer must therefore have a structure analogous to that of the base $C_{23}H_{39}N$, m. p. 130°, obtained by reaction of dimethylamine with the toluene-*p*-sulphonyl ester of 3β-hydroxypregn-5-ene. The second isomer, $C_{22}H_{35}N$, gave an acetyl derivative, m. p. 182—183°, identical with the acetylmethylaminopregnadiene obtained by degradation of conessine as described in the preceding paper. This base is designated as 3β-methylaminopregna-5 : 20-diene (I; R = NHMe, R′ = CH:CH_2) because methylation and catalytic hydrogenation gave 3β-dimethylamino*allo*pregnane (V; R = NMe_2, R′ = Et) and because of the identity of the acetyl derivative with the conessine degradation product. As already shown, the latter contains the original conessine double bond, which on the basis of the physical evidence is situated at position 5 : 6; a 3 : 5-*cyclo*-structure analogous to (II) or (III) may therefore be excluded for the second isomer.

The reaction between cholesteryl toluene-*p*-sulphonate (I; R = *p*-O·SO_2·C_6H_4·CH_3, R′ = C_8H_{17}) and liquid ammonia has been described by Julian, Magnani, Meyer, and Cole (*loc. cit.*) who obtained 3β-aminocholest-5-ene * (I; R = NH_2, R′ = C_8H_{17}) and 6ξ-amino-3 : 5-*cyclo*cholestane (II; R = C_8H_{17}). On repetition of this experiment, in addition to the two products named, we have also obtained a third isomeric base, m. p. 90—91°. The constitution of the base is not yet known, but it seems possible that it may be analogous to the bases of unknown constitution obtained in the pregnane series (see above). Related secondary and tertiary bases, $C_{28}H_{49}N$ and $C_{29}H_{51}N$, of unknown structure, were obtained by using methylamine or dimethylamine respectively in place of ammonia in the above experiment; the reaction between dimethylamine and cholesteryl toluene-*p*-sulphonate also yielded 3β-dimethylaminocholest-5-ene (I; R = NMe_2, R′ = C_6H_{17}). All three bases of unknown structure, like the known 6ξ-amino-3 : 5-*cyclo*cholestane, gave a negative iodate reaction when tested as described on p. 1110. The dimethylamino-compound, $C_{29}H_{51}N$, of unknown constitution like the isomeric 3β-dimethylaminocholest-5-ene, gave



(IV)



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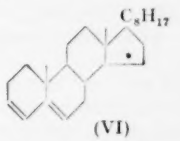

(VI)

cholesta-3 : 5-diene (VI) on Hofmann degradation. Catalytic hydrogenation gave a dihydro-derivative, $C_{29}H_{53}N$, which resisted further Hofmann degradation and was not identical with 3β- (Dodgson and Haworth, *loc. cit.*) or 3α-dimethylaminocholestane (IV; R = NMe_2, R′ = C_8H_{17}) obtained by the action of dimethylamine on cholestan-3β-yl toluene-*p*-sulphonate (V; R = *p*-O·SO_2·C_6H_4Me, R′ = C_8H_{17}), a Walden inversion being assumed to occur here as in the case of the preparation of the corresponding *allo*pregnane base.

The Hofmann decomposition of quaternary ammonium hydroxides proceeds by a bimolecular elimination mechanism, and hence in alicyclic compounds the quaternary centre must be *trans* to the hydrogen attached to a β-carbon atom (*inter alia*, Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093). Owing, however, to the preferred

* Described by Julian *et al.* as "cholesterylamine." The structure assigned here follows readily from the analogous preparation of, and the structural relation to, 3β-dimethylaminocholest-5-ene (Dodgson and Haworth, *loc. cit.*; see also below). The configurations tentatively assigned to 3β-dimethylamino-cholest-5-ene and -cholestane are confirmed by work described in this paper, particularly the preparation of 3α-dimethylaminocholestane, and the evidence from the Hofmann elimination.

conformation of the *trans*-A/B steroid molecule, a 3α-(polar) substituent, either *trans*-hydrogen atom in the β-position (at $C_{(2)}$ or $C_{(4)}$) and the two intervening carbon atoms together form a *coplanar* arrangement, and this is not so in the case of 3β-(equatorial) substituents. Since bimolecular 1 : 2-elimination reactions are particularly favoured by such a coplanar arrangement, 3α-substituents in the cholestane and *allo*pregnane nucleus should undergo bimolecular elimination more readily than the 3β-epimers (cf. Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Barton, *Experientia*, 1950, **6**, 316; *J.*, 1951, 1048). We have found this to be the case for Hofmann decomposition of the epimeric 3α- and 3β-trimethylammonium hydroxides of *allo*pregnane and cholestane. A good yield of unsaturated hydrocarbon was obtained in each case with the 3α-compounds, but scarcely any with the 3β-epimers, the original bases being recovered instead in high yield. This work therefore furnishes two excellent examples of the stereochemical specificity of the Hofmann reaction.

Experimental

*Action of Dimethylamine on Pregn-5-en-3β-yl Toluene-*p*-sulphonate.*—3β-Hydroxypregn-5-ene (I; R = OH, R′ = Et) prepared by Huang-Minlon's method (*loc. cit.*) (0·35 g.) was treated at 60° for 30 min. with toluene-*p*-sulphonyl chloride (0·35 g.) and pyridine (1·5 c.c.), and the mixture kept overnight at room temperature. The resultant *pregn-5-en-3β-yl toluene-*p*-sulphonate* separated from ether–light petroleum (b. p. 40—60°) in colourless needles (0·35 g.), $[\alpha]_D$ −52° (in $CHCl_3$, *c* 1·3), m. p. 111—113° (Found : C, 73·7; H, 8·8. $C_{28}H_{40}O_3S$ requires C, 73·7; H, 8·8%). This compound (0·32 g.) was heated overnight with dimethylamine (7 c.c.), at 100° in a small glass-lined autoclave. The excess of dimethylamine was then allowed to evaporate, and the residue treated with ester and dilute sodium hydroxide solution. The ethereal extract was washed with water, a slight excess of 3N-hydrochloric acid added, and the gelatinous precipitated hydrochloride collected. Only a little unchanged ester was recovered from the filtrate. The *base* (0·16 g.) from the hydrochloride separated from acetone in colourless plates, m. p. 130° (Found : N, 4·4. $C_{23}H_{39}N$ requires N, 4·2%). No other compound was obtained from the mother-liquids.

Reduction of the foregoing base. The base (50 mg.) in glacial acetic acid (10 c.c.) was shaken in hydrogen with Adams's platinum oxide catalyst (35 mg.) at 170°/748 mm. Hydrogen uptake (11 c.c. Calc. for one double bond and the catalyst : 11 c.c.) was complete in 30 min. The dihydro-base, isolated in the usual way and recrystallised from acetone, had m. p. 78—79°, undepressed on admixture with the base, $C_{23}H_{41}N$, obtained from 3β-hydroxypregn-5 : 20-diene (see below).

*3α-Dimethylamino*allo*pregnane* (IV; R = NMe_2, R′ = Et).—3β-Hydroxy*allo*pregnane (V; R = OH, R′ = Et), m. p. 134—136°, was prepared essentially by Huang-Minlon's method (*loc. cit.*). The *toluene-*p*-sulphonate* separated from ether–light petroleum (b. p. 40—60°) in prisms, $[\alpha]_D$ −2° (in $CHCl_3$, *c* 1·3), m. p. 110—111° (Found : C, 73·4; H, 9·2. $C_{28}H_{42}O_3S$ requires C, 73·5; H, 9·3%). This compound (0·24 g.) on treatment with dimethylamine at 100° in the manner described above gave rectangular plates (from acetone) of *3α-dimethylamino*allo*pregnane* (0·12 g.), $[\alpha]_D$ +16° (in $CHCl_3$, *c* 1·5), m. p. 108—110° (Found : C, 82·9; H, 12·3; N, 3·9. $C_{23}H_{41}N$ requires C, 83·4; H, 12·4; N, 4·2%).

*3β-Dimethylamino*allo*pregnane* (V; R = NMe_2, R′ = Et).—*allo*Pregnan-3-one was prepared by oxidation of 3β-hydroxy*allo*pregnane (V; R = OH, R′ = Et) (Ruzicka, Meister, and Prelog, *loc. cit.*). The *oxime* formed colourless prisms (from ethanol), $[\alpha]_D$ +19° (in $CHCl_3$, *c* 1·9), m. p. 196—197° (Found : C, 79·0; H, 11·0; N, 4·1. $C_{21}H_{35}ON$ requires C, 79·5; H, 11·0; N, 4·4%). To a refluxing solution of the oxime (0·45 g.) in dry technical amyl alcohol (50 c.c.) was added sodium (3·5 g.) during 2 hours; the crude primary base from the reaction mixture was methylated by 3 hours' heating on the water-bath with formic acid (0·25 c.c. of 90%), water (0·5 c.c.), and formaldehyde (0·35 c.c. of 40%). *3β-Dimethylamino*allo*pregnane* (0·20 g.) separated from acetone in colourless needles, $[\alpha]_D$ +14° (in $CHCl_3$, *c* 1·7), m. p. 96° (Found : C, 83·2; H, 12·3; N, 4·4. $C_{23}H_{41}N$ requires C, 83·3; H, 12·5; N, 4·2%), undepressed on admixture with the base of the same m. p. obtained by degradation of conessine (see Part IV, *loc. cit.*).

*Hofmann Decomposition of 3β- and 3α-Dimethylamino*allo*pregnanes.*—3β-Dimethylamino-*allo*pregnane (0·1 g.) was refluxed in acetone with excess of methyl iodide for 2 hours; the solvents were then evaporated and the residue, after being washed with ether, dissolved in aqueous methanol and shaken overnight with excess of silver oxide. The methohydroxide solution was evaporated, finally at 15 mm., and the residue distilled at 200° (bath temp.)/0·005

mm. The distillate was separated into crystalline basic (50 mg.) and neutral fractions (4 mg.). Recrystallisation of the basic fraction from acetone gave colourless needles of 3β-dimethylamino-*allo*pregnane, m. p. 96°. The neutral fraction on recrystallisation from methanol gave colourless plates, m. p. 80°, of *allo*pregn-2- or -3-ene.

A similar experiment with 3α-dimethylamino*allo*pregnane (0·30 g.) returned the base (25 mg.), m. p. 108—110°, after recrystallisation from acetone; the neutral fraction (100 mg.) of the reaction product on crystallisation from methanol gave the *allo*pregnene as colourless plates, $[\alpha]_D$ +67° (in $CHCl_3$, *c* 1·5), m. p. 81—82° (Found: C, 88·0; H, 11·8. $C_{21}H_{34}$ requires C, 88·1; H, 11·9%), undepressed on admixture with the product obtained from 3β-dimethylamino*allo*-pregnane, but depressed to 75—76° on admixture with *allo*pregnane, m. p. 84°.

Reduction of the allo*Pregnene, m. p.* 81—82°.—The hydrocarbon (11 mg.) dissolved in glacial acetic acid (1 c.c.) and ether (1 c.c.) was shaken in hydrogen with Adams's platinum oxide catalyst (11 mg.) at 20°/750 mm. Hydrogen uptake (3·0 c.c. Calc. for one double bond and the catalyst: 3·3 c.c.) was complete in 5 min. The product on crystallisation from methanol gave characteristic colourless prisms of *allo*pregnane, m. p. 83—84°, undepressed on admixture with an authentic specimen.

*Action of Methylamine on Pregna-5:20-dien-3β-yl Toluene-*p*-sulphonate* (I; R = *p*-O·SO_2·C_6H_4Me, R′ = CH:CH_2).—The toluene-*p*-sulphonyl ester (Julian, Meyer, and Printy, *loc. cit.*) (1·42 g.) was treated with methylamine at 100° for 12 hours as above and yielded a mixture of bases (0·717 g.), m. p. 89—100°, after recrystallisation from acetone. The collected product was dissolved in benzene (40 c.c.) and chromatographed on alumina (Spence's Type H, activated for 10 min. at 160—170°; 20 g.), benzene followed by chloroform being used as eluants. Three fractions were obtained: (*a*) a pasty solid (10%); (*b*) a white solid (80%); (*c*) a white solid (10% of total).

Fraction (*a*) on further chromatography yielded uncrystallisable oils and traces of fraction (*b*). Fraction (*b*) on repeated crystallisation from acetone gave a *base* as colourless plates, m. p. 108—109° (Found: C, 83·9; H, 11·5; N, 4·4. $C_{22}H_{35}N$ requires C, 84·4; H, 11·2; N, 4·5%), yielding an N-*acetyl* derivative which separated from light petroleum (b. p. 40—60°) in colourless plates, m. p. 113—114° (Found: C, 80·9; H, 10·3. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·5%).

Fraction (*c*) on recrystallisation from acetone yielded 3β-methylaminopregna-5:20-diene (I; R = NHMe, R′ = CH:CH_2) as colourless needles, m. p. 114—115°, which on acetylation gave 3β-N-*acetyl*-N-*methylaminopregna*-5:20-*diene* (I; R = NMeAc, R′ = CH:CH_2) as needles (from light petroleum, b. p. 40—60°), m. p. 182—183° [Found (on very small quantity): C, 80·4; H, 9·7. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·5%], undepressed on admixture with the acetyl derivative of the same m. p. obtained by degradation of conessine.

The base from fraction (*b*) (35 mg.) was methylated by 3·5 hours' heating at 100° with formic acid (0·2 c.c. of 90%) and formaldehyde (0·1 c.c. of 35%). The tertiary base, purified by vacuum-sublimation (30 mg.), was dissolved in acetic acid (5 c.c.), and the solution shaken in hydrogen with Adams's platinum oxide catalyst (10 mg.) at 17°/760 mm. Hydrogen uptake (7·5 c.c. Calc. for two double bonds and the catalyst: 6·5 c.c.) was complete in 6 hours. The *tetrahydro*-derivative (30 mg.), isolated in the usual way, was purified by sublimation at 180° (bath temp.)/0·1 mm., followed by crystallisation from acetone; colourless plates, m. p. 77—79·5° (Found: C, 83·0; H, 12·2. $C_{23}H_{41}N$ requires C, 83·3; H, 12·4%), were obtained, giving no depression in m. p. on admixture with the base, m. p. 78—79°, obtained as above from pregn-5-en-3β-yl toluene-*p*-sulphonate and dimethylamine, followed by catalytic hydrogenation.

Methylation and reduction in a similar manner of the 3β-methylaminopregna-5:20-diene (15 mg.) from fraction (*c*) gave 3β-dimethylamino*allo*pregnane (12 mg.), m. p. 92—93·5°, undepressed with the base, m. p. 95—96°, obtained by degradation of conessine.

*Action of Ammonia on Cholesteryl Toluene-*p*-sulphonate.*—Cholesteryl toluene-*p*-sulphonate (I; R = *p*-C_6H_4Me·SO_2·O, R′ = C_8H_{17}) (17 g.) and liquid ammonia (200 c.c.) were heated at 100° for 8 hours, excess of ammonia allowed to evaporate, and the resulting basic mixture separated into (*a*) bases with hydrochlorides insoluble in ether (5 g.), and (*b*) bases with hydrochlorides soluble in ether (6 g.) (cf. Julian, Magnani, Cole, and Meyer, *loc. cit.*). Bases (*a*) were chromatographed in light petroleum (b. p. 40—60°) on alumina (Spence Type H, activated at 160° for 10 min.; 150 g.), elution being carried out successively with light petroleum (b. p. 40—60°), ether–light petroleum (b. p. 40—60°), ether, and chloroform. There were thus obtained 3β-aminocholest-5-ene (I; R = NH_2, R′ = C_8H_{17}) (2 g.), which on recrystallisation from ether formed needles, m. p. 90—91° (Julian *et al.*, *loc. cit.*, give m. p. 89—94°, $[\alpha]_D$ −26°), and, in the final eluates, a base (2·5 g.) recrystallising from light petroleum (b. p. 40—60°) in needles, m. p. 190°, which is being examined further.

From bases (*b*) was obtained 6ξ-amino-3 : 5-*cyclo*cholestane (II; R = C_8H_{17}) as colourless rosettes (from hexane), m. p. 77—79° (Julian *et al.*, *loc. cit.*, give m. p. 77—79°).

Action of Methylamine on Cholesteryl Toluene-p-*sulphonate.*—The ester (10 g.) and methylamine (10 c.c.) were heated at 100° for 8 hours, and the crude basic product (3·7 g.; from ether-insoluble hydrochloride) chromatographed essentially in the manner described above, yielding (*a*) a *base* (2·2 g.), m. p. 84—86°, and (*b*) a base (50 mg.), m. p. 109—113°, in addition to oily fractions. Fraction (*a*) on recrystallisation from acetone gave colourless needles, m. p. 85·5—86·5° (Found: C, 84·1; H, 12·3; N, 3·1. $C_{28}H_{49}N$ requires C, 84·1; H, 12·4; N, 3·5%).

Methylation of the base $C_{28}H_{49}N$, *m. p.* 85·5—86·5°. The base (310 mg.) was methylated in the usual manner with formic acid (1·4 c.c. of 90%) and formaldehyde (0·2 c.c. of 40%) for 4 hours at 100°. The product (300 mg.) separated from acetone in colourless plates, m. p. 69—70°, undepressed on admixture with the base $C_{29}H_{51}N$, m. p. 70—71°, obtained as described below by the action of dimethylamine on cholesteryl toluene-*p*-sulphonate.

Action of Dimethylamine on Cholesteryl Toluene-p-*sulphonate.*—The sulphonate (10 g.) and dimethylamine (9 c.c.) were heated at 100° for 8 hours, and the crude bases (5 g. from hydrochlorides insoluble in ether) chromatographed as above, yielding successively (*a*) an oil (0·1 g.), (*b*) a colourless solid, m. p. 66—69° (4 g.), and (*c*) a colourless solid, m. p. 151·5—152° (0·6 g.). Recrystallisation of fraction (*b*) from acetone gave the *base* as colourless plates, m. p. 70—71° (Found: C, 84·2; H, 12·1; N, 3·7. $C_{29}H_{51}N$ requires C, 84·2; H, 12·5; N, 3·4%). Fraction (*c*) was recrystallised from ether and yielded colourless neeeles of 3β-dimethylaminocholest-5-ene (I; R = NMe_2, R′ = C_8H_{17}), $[\alpha]_D$ −32° (in $CHCl_3$, *c* 0·5), m. p. 151·5—152° undepressed on admixture with an authentic speciman. Dodgson and Haworth (*loc. cit.*) give m. p. 151°, $[\alpha]_D$ −31·5° (in $CHCl_3$, *c* 0·5). Catalytic hydrogenation according to Dodgson and Haworth's method gave 3β-dimethylaminocholestane, m. p. 105—106°. Separation of the above two bases may also be effected by fractional crystallisation of the hydrochlorides from methanol. A similar mixture is produced by heating cholesteryl toluene-*p*-sulphonate (11·9 g.), ethanol (15 c.c.), toluene-*p*-sulphonic acid (3 g.), and dimethylamine (13·5 g.) for 24 hours at 120° (we thank Dr. G. H. Whitfield for this experiment) or, significantly, by methylating with formaldehyde and formic acid the basic mixture (from hydrochlorides insoluble in ether), obtained as above by the action of ammonia on cholesteryl toluene-*p*-sulphonate.

Hofmann Degradation of 3β-*Dimethylaminocholest*-5-*ene.*—*Cholest*-5-*ene*-3β-*trimethylammonium iodide* (I; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol as a colourless microcrystalline powder, $[\alpha]_D$ −20° (in $CHCl_3$ *c* 2·0), m. p. 295—298° (decomp.) (Found: N, 2·3; I, 23·0. $C_{30}H_{54}NI$ requires N, 2·5; I, 22·8%). An aqueous solution of the corresponding methohydroxide was evaporated and heated to 180° (bath-temp.) at 0·1 mm. Recrystallisation of the sublimate from ether–methanol gave colourless needles of cholesta-3 : 5-diene (VI), m. p. 77—78°, undepressed on admixture with an authentic specimen.

Hofmann Degradation of the Base, $C_{29}H_{51}N$, *m. p.* 70—71°.—The base (116 mg.) yielded a *methiodide* (158 mg.), which separated from aqueous alcohol in colourless needles, m. p. 270—272° (decomp.) (Found: C, 65·0; H, 9·9; N, 2·4; I, 22·4. $C_{30}H_{54}NI$ requires C, 64·8; H, 9·8; N, 2·5; I, 22·8%). This salt (55 mg.) was converted into an aqueous solution of the corresponding methohydroxide, which was evaporated and heated at 160° (bath-temp.)/0·1 mm. The white sublimate (32 mg.) of cholesta-3 : 5-diene had m. p. 77—78°, undepressed on admixture with an authentic specimen. No basic material was isolated. A similar result was obtained by heating the quaternary iodide (100 mg.) with water (2·4 c.c.), ethylene glycol (27 c.c.), and potassium hydroxide (4 g.) at the reflux temperature (140°) for 4 hours.

Reduction of the base, $C_{29}H_{51}N$, *m. p.* 70—71°. The base (317 mg.) was shaken in glacial acetic acid (7 c.c.), in hydrogen at 19°/769 mm. in the presence of Adams's platinum oxide catalyst (25 mg.). Hydrogen uptake (24 c.c. Calc. for one double bond and the catalyst: 23·4 c.c.) was complete in 6 hours. The *dihydro-base* (320 mg.), isolated in the usual way, separated from acetone as colourless plates, m. p. 73—74° (Found: C, 83·3; H, 12·6; N, 3·9. $C_{29}H_{53}N$ requires C, 83·8; H, 12·9; N, 3·4%), depressed to 58° on admixture with the original base, m. p. 70—71°. The reduced base was recovered unchanged on attempted Hofmann degradation, no non-basic product being isolated.

Attempted isomerisation of the base $C_{29}H_{51}N$, *m. p.* 70—71°. The base (500 mg.) and dimethylammonium toluene-*p*-sulphonate (500 mg.) were heated with dimethylamine (10 c.c.) for 12 hours at 108°. The recovered base (485 mg.) had m. p. 69—70°, raised to 70—71° on recrystallisation from acetone. No depression in m. p. was observed on admixture with the original base.

3α-*Dimethylaminocholestane* (IV; R = NMe_2, R′ = C_8H_{17}).—Cholestan-3β-yl toluene-*p*-

sulphonate (V; R = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$, R′ = C_8H_{17}) (0·25 g.), prepared by Stoll's method (*loc. cit.*), was heated with dimethylamine (6 c.c.) at 100° for 8 hours. The basic product (100 mg.) was recrystallised from acetone, and the 3α-*dimethylaminocholestane* thus obtained as colourless plates, $[\alpha]_D$ +22° (in $CHCl_3$, *c* 2·0), m. p. 90·5—91·5° (Found: C, 84·0; H, 12·8. $C_{29}H_{53}N$ requires C, 83·8; H, 12·9%).

Hofmann Decomposition of 3α- *and* 3β-*Dimethylaminocholestanes.*—3α-*Cholestanyltrimethylammonium iodide* (IV; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol in colourless needles, m. p. 289—290° (decomp.) (Found: C, 64·8; H, 10·1. $C_{30}H_{56}NI$ requires C, 64·6; H, 10·1%). The quaternary iodide (161 mg.) was converted into methohydroxide in the usual way, and the aqueous methanolic solution evaporated and heated at 160—180° (bath-temp.)/0·5 mm. for 30 min. The mixture was extracted with ether, and the residue from the ether separated into a basic (20 mg.) and a non-basic fraction (85 mg.). The former had m. p. 90—91°, undepressed on admixture with 3α-dimethylaminocholestane; the latter began to melt at 58° (Found: C, 87·1; H, 12·4. Calc. for $C_{27}H_{46}$: C, 87·5; H, 12·5%), and had $[\alpha]_D$ +63° (in $CHCl_3$, *c* 2·0); it appeared to be a mixture of cholest-2-ene, m. p. 74·5—75°, $[\alpha]_D$ +69° (in $CHCl_3$, *c* 1·6), and cholest-3-ene, m. p. 72—72·5°, $[\alpha]_D$ +57° (in $CHCl_3$, *c* 1·4) (Barton and Rosenfelder, *J.*, 1951, 1048). Hydrogenation of the mixture (40 mg.) in ether (2 c.c.) and glacial acetic acid (5 c.c.) in the presence of Adams's platinum oxide catalyst (13 mg.) was complete in 8 hours (Hydrogen uptake, 5·3 c.c. Calc. for one double bond and the catalyst: 5·5 c.c.). The crude hydrogenation product (40 mg.) had m. p. 75° and, after recrystallisation from ether–ethanol, colourless plates of cholestane were obtained, $[\alpha]_D$ +26° (in $CHCl_3$, *c* 2·0), m. p. 78—79°. Barton and Cox (*J.*, 1948, 783) give m. p. 80°, $[\alpha]_D$ +25° (in $CHCl_3$, *c* 1·5).

3β-*Cholestanyltrimethylammonium iodide* (V; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol as a colourless, microcrystalline powder, m. p. 290° (decomp.), $[\alpha]_D$ +33° (in $CHCl_3$, *c* 1·1) (Found: I, 20·7. $C_{30}H_{56}NI$ requires I, 22·8%). Attempted Hofmann decomposition of this salt (170 mg.) in the manner described above gave a mixture of a neutral oil (5 mg.), which was not examined further, and a base (117 mg.), m. p. 103—104°, raised to 105—106° on recrystallisation from ether. No depression in m. p. was observed on admixture with 3β-dimethylaminocholestane. A similar result was obtained by heating the methiodide (100 mg.) with water (2·4 c.c.), ethylene glycol (27 c.c.), and potassium hydroxide (4 g.) for 4 hours at 140°.

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225. *The Constitution of Conessine. Part VI.* The Heterocyclic Ring.*

By H. FAVRE, R. D. HAWORTH, J. MCKENNA, R. G. POWELL, and G. H. WHITFIELD.

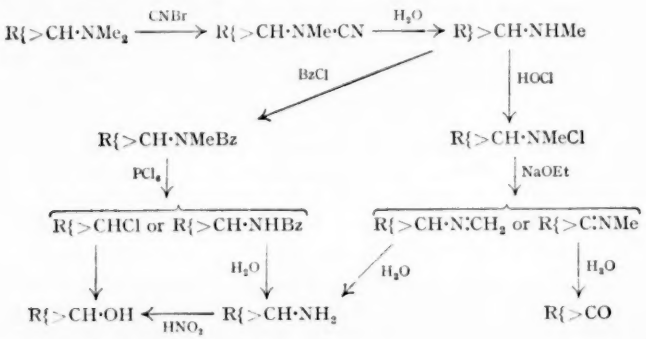
Attempts to replace the dimethylamino-group of hexahydro*apo*conessine by oxygen functions are described. *apo*Conessine and other methine bases related to conessine are cyclised by heating them in neutral or alkaline solution, and the nature of this reaction is discussed. Evidence is presented relating to the mechanism of *hetero*conessine formation, and to the structure of the conessine heterocyclic ring. Preliminary experiments on tetramethylholarrhimine are described, and molecular-rotation differences in the conessine field are briefly discussed.

THE work described in the two foregoing papers has led to the establishment of the positions in the conessine molecule of the dimethylamino-group and double bond. The

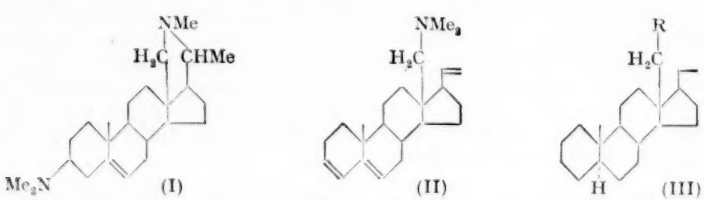
* Part V, preceding paper.

present paper describes a variety of experiments which bear on the structural position around the heterocylic ring, and includes observations on the chemistry of *hetero*conessine (Haworth, McKenna, and Whitfield, *J.*, 1949, 3127) and holarrhimine (Siddiqui *et al.*, *J. Indian Chem. Soc.*, 1932, **9**, 553, and later papers; Bertho, *Ber.*, 1947, **80**, 316). A discussion on molecular-rotation data in the conessine field is appended.

It follows from earlier work that the methylimino-group of the heterocyclic ring in the conessine molecule is attached to either $C_{(20)}$ or $C_{(21)}$ and some other carbon atom in the neighbourhood to which is also attached the dimethylamino-group in *apo*conessine. A series of degradation studies was accordingly planned with hexahydro*apo*conessine, the ultimate aim of which was to replace the dimethylamino-group by an oxygen function (ketonic or alcoholic), the position of which might then be recognised. The reactions evisaged are indicated in the annexed scheme, in which the tertiary amino-group is assumed to be attached to a methylene or methine carbon atom ($R = C_{20}H_{34}$). Formula (I) for conessine, proposed in an earlier note (Haworth, McKenna, Powell, and Whitfield, *Chem. and Ind.*, 1952, 215) and utilised in Part IV (*J.*, 1953, 1102), will be employed also in this paper, where arguments in favour of the heterocyclic arrangement shown are developed. On this basis *apo*conessine will have structure (II), and hexahydro*apo*conessine structure (III; $R = NMe_2$).



After some experience with *cyclo*hexyldimethylamine, which was degraded to methyl-*cyclo*hexylamine and *cyclo*hexanone, by the cyanogen bromide–hypochlorous acid procedure (cf. von Braun, *Ber.*, 1900, **33**, 1438, 2730; Hellerman and Sanders, *J. Amer. Chem. Soc.*, 1927, **49**, 1742; Julian, Magnani, Meyer, and Cole, *ibid.*, 1948, **70**, 1834), a similar series of reactions was attempted with hexahydro*apo*conessine. The base did not combine readily with cyanogen bromide, but in boiling benzene solution (Winterfield, *Ber.*, 1931, **64**, 137, 150) *N*-cyano-*N*-demethylhexahydro*apo*conessine (III; R = NMe·CN) was formed, which on hydrolysis with aqueous-alcoholic hydrochloric acid gave *N*-demethylhexahydro*apo*conessine (III; R = NHMe) characterised by its *N*-acetyl, *N*-benzoyl, and *N*-nitroso-derivatives. Methylation with formaldehyde and formic acid gave back hexahydro*apo*conessine.

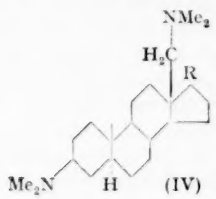


Treatment of *N*-demethylhexahydro*apo*conessine with ethereal hypochlorous acid gave *N*-chloro-*N*-demethylhexahydro*apo*conessine (III; R = NClMe) from which, how-

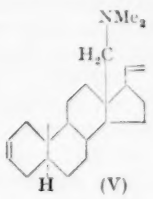
ever, no primary base or ketone could be obtained on treatment with alcoholic sodium ethoxide followed by acid hydrolysis. The primary amino*allo*pregnane (III; R = NH_2), however, was obtained by treatment of the benzoyl derivative of the secondary amine (III; R = NMeBz) with phosphorus pentachloride (cf. von Braun, *Ber.*, **1904**, **37**, 2812, 2915, 3210, 4581) followed by hydrolysis of the product with hydrochloric acid. The primary base gave an *N*-acetyl derivative; a Zerewitinoff determination showed the presence of two active hydrogen atoms, but the base did not react with benzaldehyde. Methylation with formaldehyde and formic acid gave back hexahydro*apo*conessine. Treatment of the primary amine with nitrous acid followed by oxidation of the reaction mixture with chromic acid gave no recognisable product, and these experiments were accordingly abandoned.

The preparation of *hetero*conessine in small yield by treatment of conessine dimethiodide with potassium hydroxide in ethylene glycol solution has been described in Part II (Haworth, McKenna, and Whitfield, *loc. cit.*), but a considerable increase in yield may be obtained by using the modified conditions described on p. 1126. Since this isomer of conessine on reduction gives the base dihydro*hetero*conessine, which may also be obtained from dihydroconessine by decomposition of the dimethohydroxide in alkaline glycol (Part II, *loc. cit.*), it was evident that the isomerisation change does not involve the double bond. A close relationship between conessine and *hetero*conessine was indicated by the oxidation of *hetero*conessine to dioxy*hetero*conessine, analogous to dioxyconessine, by the infra-red absorption curve of the base which shows maxima at 799, 831, and 1660 cm.$^{-1}$ as required for a 5 : 6-double bond (cf. the conessine infra-red curve discussed in Part IV), and by the optical-rotation data presented below. Hofmann decomposition of *hetero*conessine gave *apo*conessine, indicating that the point or points of dissimilarity between the two bases are removed by elimination of the dimethylamino-group and/or fission of the heterocyclic ring. Hofmann decomposition of dihydro*hetero*conessine dimethohydroxide gave the methine base,* $C_{25}H_{44}N_2$, previously obtained from dihydroconessine (Haworth, McKenna, and Whitfield, *loc. cit.*; Haworth, McKenna, Powell, and Woodward, *loc. cit.*); this base may now be designated as 5 : 6-dihydroconessimethine (IV; R = $CH{:}CH_2$). It follows that the dissimilarity between conessine and *hetero*conessine (or between the dihydro-derivatives) involves the arrangement around the heterocyclic ring only, and disappears on ring fission.

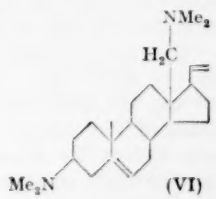
This conclusion was confirmed by partial Hofmann degradation of conessine and of *hetero*conessine. Decomposition of conessine dimethohydroxide in alkaline glycol solution, at a temperature higher than that found to give a favourable yield of *hetero*conessine, gave a diacid base, $C_{25}H_{42}N_2$, m. p. 79°, in addition to the monomethiodide, $C_{22}H_{33}N,CH_3I$, previously described (Haworth, McKenna, and Whitfield, *loc. cit.*). This base was formulated as conessimethine (VI) because it was cyclised in boiling glacial acetic acid, and the structure was confirmed by preparation of conessimethine by a different route (Haworth, McKenna, and Whitfield, *J.*, 1953, 1102). *hetero*Conessine dimethiodide on similar treatment also yielded conessimethine, in agreement with the conclusion already reached on the relation between *hetero*conessine and conessine.



(IV)



(V)

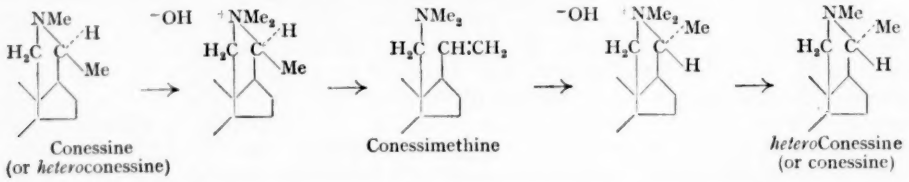


(VI)

Our first tentative hypothesis on the mechanism of formation of *hetero*conessine was that an inversion of configuration had taken place at an asymmetric centre to which the

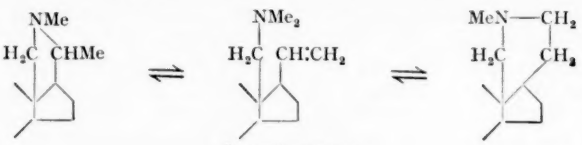
* A small quantity of a monoacid base, either 5 : 6-dihydro*apo*conessine or an isomer (V), was also attained.

ring-nitrogen atom was attached, *e.g.*, $C_{(20)}$ in (I). Such an epimeric change might conceivably have taken place by labilisation of a hydrogen atom at the asymmetric centre by the attached quaternary nitrogen (in the metho-salt), but we appreciated the theoretical objections to this possibility, and indeed recently Doering and Meislich (*J. Amer. Chem. Soc.*, 1952, **74**, 2099) have adduced strong evidence against it. An alternative mechanism was however perceived. The isomerisation reaction involves the heterocyclic ring, and a structure epimeric with that of conessine at $C_{(20)}$ [on the basis of (I)] could be produced from conessine dimethiodide if the ring first opened to give conessimethine (VI) (normal Hofmann decomposition) and subsequently *closed* again by the addition of the elements of water (*i.e.*, a reversal of the Hofmann reaction); loss of methyl alcohol from the quaternary salt would then give the isomeric base :



Conessine (or *hetero*conessine) — Conessimethine — *hetero*Conessine (or conessine)

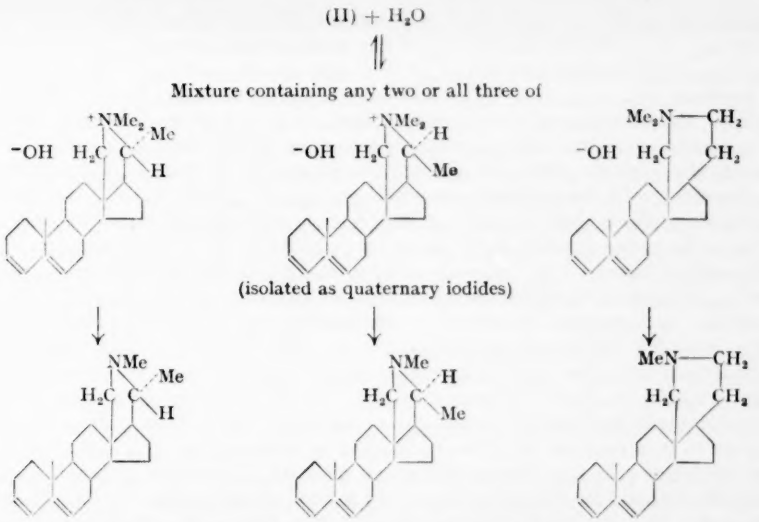
Again, the possibility being granted of such a reaction sequence, conessine and *hetero*-conessine might also be formulated as structural isomers, the methylimino-group engaging $C_{(20)}$ in one of the bases and $C_{(21)}$ in the other. No strictly comparable cyclisation reaction of an unsaturated tertiary amine to quaternary salt by heating in *alkaline* solution is on record, although cyclisation in acid solution is well known both with methine bases in the conessine series and in numerous other cases (for reference, see Haworth, McKenna, Powell, and Woodward, *loc. cit.*), and Pyman (*J.*, 1913, **103**, 817) prepared tetrahydroberberine methohydroxide by heating anhydromethylcanadine (which contains an unsaturated ten-membered ring) in aqueous alcohol. It was found, however, that *apo*conessine was cyclised when heated in aqueous glycol to about 150°, with or without the addition of potassium hydroxide; a quaternary salt (isolated as iodide) was produced along with an oily base. A similar result was obtained by heating *apo*conessine in aqueous ethanol solution at 150°. Evidence of non-homogeneity of the methiodides thus formed was obtained on fractional crystallisation, but in all cases the main fractions * obtained after several crystallisations appeared to be identical with one another and with the mono-



Conessimethine

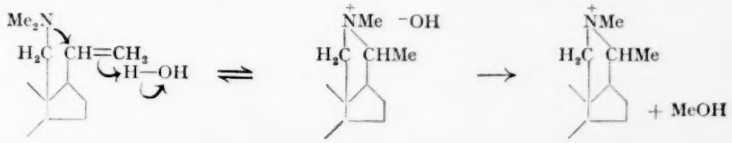
methiodides * obtained by cyclisation of *apo*conessine in glacial acetic acid or by treatment of conessine dimethiodide in alkaline glycol (Haworth, McKenna, Powell, and Woodward, *loc. cit.*). One may thus infer that ring closure of *apo*conessine, at least in alkaline solution, takes place in more than one way. The oily monoacid bases (evidently also mixtures) accompanying the methiodides were not methines, as they did not react as such with acetic acid, and they were clearly formed by loss of methyl alcohol from the corresponding quaternary hydroxides which are the first products of the cyclisation reaction. The reactions, which are analogous to those suggested above for *hetero*conessine formation (except that the ring closure takes place in more than one way), may be represented as follows :

* There is no evidence that these are homogeneous apart from the constancy of m. p. on repeated recrystallisation. It will be evident from the work described in this paper that the argument in favour of a five-membered heterocyclic ring in conessine based on methiodide identities described in Part III (*loc. cit.*) now becomes invalid.



When 5 : 6-dihydroconessimethine (IV; R = $CH{:}CH_2$) was heated with alkaline glycol, or in 90% aqueous alcohol, cyclisation and loss of methyl alcohol took place in the same way, and the basic product of each reaction was dihydro*hetero*conessine, which was readily obtained in a pure state. Likewise treatment of conessimethine (VI) with potassium hydroxide in glycol readily gave *hetero*conessine. No conessine or dihydroconessine was formed. The formation of *hetero*conessine and dihydro*hetero*conessine in this way is in conformity with either of the two mechanisms suggested above (p. 1118) for the isomerisation of conessine and its dihydro-derivative by treatment of the dimethiodides with alkaline glycol; it is evident that the corresponding methine is first formed by ordinary Hofmann fission, and that this reaction is followed by recyclisation and loss of methyl alcohol. The isolation of only *one* basic product (the *hetero*-base) from the direct cyclisation of conessimethine or dihydroconessimethine is in contrast to the results just described for *apo*conessine, but does not necessarily imply that the cyclisation of the diacidic methines takes place in only one direction; * the *hetero*-quaternary hydroxide may undergo loss of methyl alcohol faster than any isomers produced.

A possible analogy to this cyclisation reaction is the case of unsaturated tertiary vinylamines, which are stronger bases than the corresponding saturated amines, although the reverse would normally be expected. Adams and Mahan (*J. Amer. Chem. Soc.*, 1942, **64**, 2588) have suggested that this result is explained by the formation in solution of an equilibrium proportion of quaternary hydroxide. In our case a similar reaction would result in cyclisation as follows:



Significant use may be made of the relationship established between conessine and *hetero*conessine in an analysis of the structural position around the heterocyclic ring in these two bases. The conessine methylimino-group is attached to $C_{(20)}$ or $C_{(21)}$;

* There is evidence (see p. 1127) that the *acetic acid* cyclisation of 5 : 6-dihydroconessimethine gives a mixture of quaternary salts. Low yields of quaternary salts (isolated as iodides) are also obtained after the cyclisation of the diacidic methines in alkaline solution, but these have not been examined further.

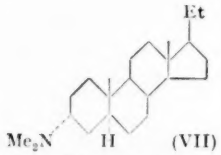
construction of models indicates that on steric grounds the other carbon atom involved is probably $C_{(18)}$, $C_{(12)}$, or (less likely) $C_{(15)}$, if the methylimino-group is also attached to $C_{(20)}$; or $C_{(18)}$, $C_{(12)}$, $C_{(16)}$, or (less likely) $C_{(15)}$, if it is also attached to $C_{(21)}$. If the methylimino-group involves $C_{(12)}$, $C_{(15)}$, or $C_{(16)}$, the steric orientation must be β. Of the various possibilities, the attachment of the ring nitrogen at $C_{(16)}$ may be excluded, since on the above evidence conessine and *hetero*conessine must either be (*a*) epimeric at $C_{(20)}$ or (*b*) structurally isomeric, with the methylimino-group attached at $C_{(20)}$ in one base and at $C_{(21)}$ in the other. Of the remaining possibilities ($C_{(12)}$, $C_{(15)}$, and $C_{(18)}$), $C_{(15)}$ appears unlikely on biogenetic grounds, and in addition the conessine and *hetero*conessine heterocyclic rings would be rather more strained than would be expected from the ready ring closure of the related methine bases. $C_{(18)}$ appears a more likely position of attachment than either $C_{(12)}$ or $C_{(15)}$ because of the failure of *apo*conessine and its hexahydro-derivative to yield any hydrocarbon on attempted Hofmann decomposition (Spath and Hromatka, *Ber.*, 1930, **63**, 126; Haworth, McKenna, and Whitfield, Part II, *loc. cit.*). The negative result has been confirmed again for each of these two bases; hexahydro*apo*conessine was recovered from the reaction in almost quantitative yield but the product obtained by pyrolysis of *apo*conessine methohydroxide was not *apo*conessine, but a base, m. p. 93—94°, which did not appear to be a methine as it was unaffected by refluxing in acetic acid. It is possible that in the latter case ring closure has taken place by a sequence of reactions similar to that described above for the formation of the *hetero*-bases, and the matter is being further investigated. The simplest interpretation of the failure of *apo*conessine and (more particularly) its hexahydro-derivative to yield any hydrocarbon on attempted Hofmann decomposition would be that neither base has a *trans*-hydrogen atom attached to the carbon atom in the β-position to the quaternary ammonium centre; thus, of the three remaining probable positions listed above for the attachment of the basic centre in *apo*conessine, $C_{(12)}$ and $C_{(15)}$ would be eliminated, leaving $C_{(18)}$.*

Additional evidence in favour of $C_{(18)}$ as a position of attachment for the basic centre, and for (I) and (III; R = NMe_2) for conessine and hexahydro*apo*conessine respectively may be derived from the Kuhn–Roth *C*-methyl results given below:

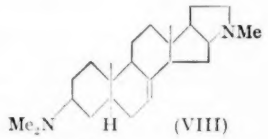
Compound	*C*-Me, %	No. of *C*-methyl groups in molecule
Conessine *	5·30	1·27
*hetero*Conessine	6·84	1·63
Hexahydro*apo*conessine	5·80	1·29
3α-Dimethylamino*allo*pregnane	9·80	2·17

* Bertho (*Annalen*, 1950, **569**, 1) reports 1·29 *C*-methyl groups in conessine.

The best interpretation of these results is that the first three compounds each contains two *C*-methyl groups; the contrasting result obtained for 3α-dimethylamino*allo*pregnane (VII, an isomer of hexahydro*apo*conessine which contains three *C*-methyl groups) is significant. On the basis of these results conessine and *hetero*conessine are not structural isomers, but are epimeric with one another at $C_{(20)}$. A model of formula (I) indicates that the heterocyclic ring is virtually strain-free, in keeping with the ready cyclisation reactions described above.



(VII)



(VIII)

The preferred position of attachment of the conessine heterocyclic ring ($C_{(18)}$) is not, in general, a position of substitution in steroids. Recently, however, it has been suggested (Jacobs and Sato, *J. Biol. Chem.*, 1951, **191**, 65; Pelletier and Jacobs, *J. Amer. Chem. Soc.*,

* The retardation of the Hofmann reaction in the case of hexahydro*apo*conessine may of course be of stereochemical origin (see Part V). It is noteworthy, however, that a steroidal 12-trimethylammonium salt has been degraded to the 11 : 12-ethylene by McPhillamy and Scholz (*J. Org. Chem.*, 1949, **14**, 643), although the steric orientation of the quaternary centre has not been proved.

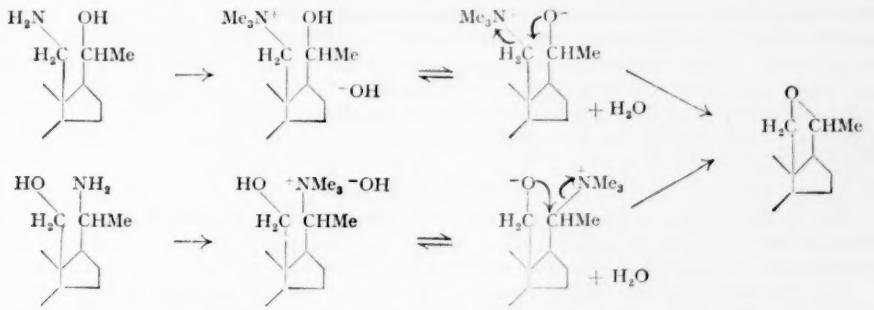
1952, **74**, 4218) that the veratrine alkaloid *iso*rubijervine is a $C_{(18)}$-hydroxylated solanidine, although the evidence is not conclusive.

In recent communications Bertho (*loc. cit.*; *Annalen*, 1951, **573**, 210) has proposed the structure (VIII) for conessine; no substantial evidence, however, is adduced in favour of this formula (compare the criticisms given in Part III), which can therefore be abandoned in view of the work described in the present series of papers.

Some preliminary experiments have been carried out with the base *N*-tetramethylholarrhimine, which was readily isolated through its insolubility in light petroleum from the alkaloidal extract of Kurchi bark after methylation. Holarrhimine contains two primary amino-groups, a hydroxyl group, and a double bond, previously characterised by the preparation of a dibromide and by iodate oxidation of *N*-tetramethylholarrhimine to a dioxy-derivative similar in properties to dioxyconessine. There has been no demonstration of the presence of a steroidal nucleus, nor has any relation been established with the heterocyclic Kurchi alkaloids, but it has been suggested (Siddiqui, *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 249) that the hydroxyl group and one amino-group of holarrhimine may correspond structurally to the bivalent imino- or methylimino-group in the other bases, a hypothesis which is attractive on biogenetic grounds provided that holarrhimine has the usual pregnane nucleus,

We have confirmed the presence of a double bond in *N*-tetramethylholarrhimine by catalytic reduction to the dihydro-derivative. Attempted dehydration of dihydro-*N*-tetramethylholarrhimine by heating it with boric oxide (cf. Prelog and Szpilfogel, *Helv. Chim. Acta*, 1944, **27**, 390) resulted in elimination of the elements of dimethylamine instead of water; the unsaturated product, $C_{23}H_{39}ON$, was reduced catalytically to a dihydro-derivative, but we have not yet been able to decide whether the unsaturation is due to the presence of a hindered carbonyl group or of an ethylenic linkage.

Hofmann decomposition of *N*-tetramethylholarrhimine resulted in elimination of both basic centres and gave a product $C_{21}H_{30}O$. The ultra-violet absorption curve of this substance strongly suggests the presence of a conjugated steroidal 3 : 5-diene system as in *apo*conessine, indicating that *N*-tetramethylholarrhimine and conessine may have the same carbon framework, and correspond in detail around rings A and B. Catalytic hydrogenation gave a mixture of tetrahydro-derivatives (of which one was obtained pure), as would be expected on reduction of a 3 : 5-diene system. The tetrahydro-mixture gave negative tests for hydroxyl, keto-, or olefinic groups, and the last two were also excluded on ultra-violet absorption evidence (no selective absorption : ε at 2000 Å was 100). The oxygen atom in the compound $C_{21}H_{30}O$ and its tetrahydro-derivatives is therefore present as a cyclic ether. Analogous formation of cyclic ethers during Hofmann decomposition of hydroxylated amines has been observed in morphine chemistry (cf. Cahn, *J.*, 1926, 2562). The ready formation of the oxygen bridge parallels the ready cyclisation of methine bases in the conessine series; on the basis of Siddiqui's proposals (cf. above), and structure (I) being used for conessine, the reactions may be represented as follows :



A list of specific and molecular rotations measured in this laboratory for the more significant conessine derivatives and related synthetic compounds is given below. Values

Substance	$[\alpha]_D$	$[M]_D$	c	Solvent
Conessine	−1°	−4°	5·6	$CHCl_3$
Conessine dimethiodide	+6	+38	2·0	MeOH
Dihydroconessine	+46	+165	3·0	$CHCl_3$
Dihydroconessine dihydriodide	+36	+221	0·9	MeOH
Dihydroconessine dimethiodide	+26	+167	2·8	,,
Chlorodihydroconessine	+25	+98	8·9	$CHCl_3$
Formaldehyde addition base, $C_{25}H_{42}ON_2$, m. p. 171—173°	+65	+251	5·4	,,
*apo*Conessine	−120	−390	2·7	,,
*apo*Conessine methiodide	−54	−253	2·3	,,
Hexahydro*apo*conessine	+48	+159	2·8	,,
Hexahydro*apo*conessine methiodide	+25	+118	2·4	,,
Methiodide, $C_{22}H_{33}N,CH_3I$, from cyclisation of apoconessine in acetic acid	−38	−171	1·3	,,
Tetrahydro-derivative of methiodide, $C_{22}H_{33}N,CH_3I$	+29	+133	1·8	,,
Conessimethine	−25	−93	1·4	,,
5 : 6-Dihydroconessimethine	+27	+101	2·9	,,
Tetrahydroconessimethine	+34	+127	3·1	,,
*neo*Conessine	+76	+270	4·7	,,
*neo*Conessine dihydriodide	+1	+6	0·6	MeOH
*neo*Conessine dimethiodide	+15	+96	1·7	,,
*neo*Conessimethine	+85	+315	1·9	$CHCl_3$
Dihydro*neo*conessimethine	+90	+335	3·3	,,
*hetero*Conessine	−25	−89	1·1	,,
*hetero*Conessine dimethiodide	+13	+83	1·0	MeOH
Dihydro*hetero*conessine	+15	+54	1·8	$CHCl_3$
Dihydro*hetero*conessine dimethiodide	+31	+200	2·0	MeOH
Tetramethylholarrhimine	−32	−124	2·1	$CHCl_3$
Benzoyltetramethylholarrhimine	−16	−79	2·5	,,
Dihydrotetramethylholarrhimine	+11	+43	2·5	,,
Cyclic ether, $C_{21}H_{30}O$	−139	−414	1·5	,,
Tetrahydro-cyclic ether	+4	+12	1·6	,,
Pregna-3 : 5 : 20-triene	−210	−592	0·3	,,
3β-Dimethylaminocholest-5-ene	−32	−132	0·5	,,
3β-Dimethylaminocholest-5-ene methiodide	−20	−111	2·1	,,
3β-Dimethylaminocholestane	+23	+95	1·1	,,
3β-Dimethylaminocholestane methiodide	+33	+184	1·1	,,
3α-Dimethylaminocholestane	+22	+91	2·1	,,
3β-Dimethylaminopregn-5-ene (*ex* conessine)	−38	−125	1·5	,,
3β-Dimethylamino*allo*pregnane (*ex* conessine)	+18	+60	2·0	,,
3α-Dimethylamino*allo*pregnane	+16	+52	1·5	,,

for most of these compounds have not been reported previously. The average probable error in specific rotation is about ±3°, corresponding to an error of about ±25° in molecular-rotation differences.

Discussion

(a) *The "Conessine Double Bond."*—The Δ values (Barton and Klyne, *loc. cit.*) calculated from the above data for the double bond in conessine, the derived 3β-dimethylaminopregn-5-ene, *hetero*conessine, tetramethylholarrhimine, and for the "conessine double bond" in conessimethine are −169°, −185°, −143°, −167°, and −194°, respectively. These values are sufficiently close to indicate that the double bond occupies the same nuclear position in all five compounds. The Δ values quoted are all lower (arithmetically) than would be expected for a double bond in the 5 : 6-position, but the agreement is closer than for any other position for which the necessary data are recorded. The Δ values for the 5 : 6-double bond in cholesterol, 3β-dimethylaminocholest-5-ene, and 3β-hydroxypregn-5-ene (Barton and Holness, *J. Amer. Chem. Soc.*, 1950, **72**, 3274) are −243°, −227°, and −229°, respectively; introduction of a dimethylamino-group at $C_{(3)}$ *or* replacement of the *iso*octyl side chain at $C_{(17)}$ by ethyl thus reduces the Δ value, and the operation of *both* factors in conessine and its derivatives may explain the low results quoted.

(b) *The* neo*Conessine Double Bond.*—The Δ value for the *neo*conessine double bond (related to dihydroconessine) is +105°, which would agree with the values for a double bond in the 7 : 8- (A/B *cis*) or 8 : 9- (A/B *trans*) positions, which are +119° and +96°, respectively. The formation of *neo*conessine from conessine, however, may involve a

deep-seated change, such as the rearrangement of the carbon skeleton,* and as the structure of the base is under active investigation, we prefer to postpone further discussion.

(c) *Other Groups.*—All compounds containing or postulated as containing the conjugated 3 : 5-diene system have high negative rotations of the order expected, but most of them are unsuitable for quantitative comparisons (cf. Barton and Klyne, *loc. cit.*). 3α- and 3β-Dimethylamino-groups have very low Δ values resembling those for the corresponding hydroxy-groups. The Δ value for the chlorine atom in chlorodihydroconessine is −67°, in good agreement with the value −71° for the halogen atom in 5-chlorocholestane (Mauthner, *Monatsh.*, 1906, **27**, 305; 1907, **28**, 1113).

Experimental

Degradation of cyclo*Hexyldimethylamine.*—A solution of the amine (Skita and Rolfes, *Ber.*, 1920, **53**, 1250) (28 g.) in dry ether (50 c.c.) was added dropwise during 2 hours to a stirred solution of cyanogen bromide (*Org. Synth.*, Vol. II, p. 30) (11·7 g.) in dry ether (50 c.c.) at 0°. The resultant *N*-cyano-compound was not purified but was directly hydrolysed by refluxing it with concentrated sulphuric acid (10 c.c.) diluted with water (30 c.c.) for 5 hours, yielding *N-cyclo*hexylmethylamine (7·5 g.), b. p. 148—150°, giving a benzoyl derivative, m. p. 84° (Skita and Rolfes, *loc. cit.*, report b. p. 148° and benzoyl derivative, m. p. 76°). A solution of this secondary amine (1·8 g.) in dry ether (25 c.c.) was treated at −10° with ethereal hypochlorous acid solution (0·02 g./c.c.; 80 c.c.) prepared by Goldschmidt's method (*Ber.*, 1913, **46**, 2728). After 10 minutes the ethereal solution was washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, dried (Na_2SO_4), and, after the addition of more ether to give a volume of 150 c.c., mixed with a solution of sodium ethoxide (from 1 g. of sodium) in ethanol (50 c.c.). After 48 hours the solution was free from active halogen, and was washed with water and concentrated to 40 c.c. (Widmer fractionating column). The residual alcoholic solution was treated with saturated alcoholic hydrogen chloride (25 c.c.), and refluxed on the water-bath for 15 minutes. The resultant neutral oil was identified as *cyclo*hexanone by the preparation of its 2 : 4-dinitrophenylhydrazone, m. p. 160°, undepressed on admixture with an authentic specimen.

*Hexahydro*apo*conessine* (III; R = NMe_2).—This base was prepared by hydrogenation of a solution of *apo*conessine in glacial acetic acid solution as described in Part II (*loc. cit.*). The yield of pure compound was not increased appreciably by substituting ethanol for acetic acid as solvent.

N-*Cyano*-N-*demethylhexahydro*apo*conessine* (III; R = NMe·CN).—A solution of hexahydro-*apo*conessine (7·4 g.) in anhydrous benzene (100 c.c.) was treated with cyanogen bromide (6 g.) and refluxed for 2 hours with exclusion of moisture. A further 6 g. of cyanogen bromide was added, and the refluxing continued for another 2 hours. Solvent and excess of cyanogen bromide were removed under reduced pressure, and the residue was extracted (Soxhlet) for 11 hours with light petroleum (b. p. 40—60°). The extracted solid was dissolved in benzene, and the solution washed with dilute hydrochloric acid and water, and evaporated. The residue was triturated with boiling light petroleum (b. p. 40—60°) to remove colour, and then crystallised from ethanol; the N-*cyano*-compound (III; R = NMe·CN) was thus obtained as colourless, rectangular needles (4·5 g.), m. p. 150—151° (Found: C, 80·5; H, 11·1; N, 8·4. $C_{23}H_{38}N_2$ requires C, 80·7; H, 11·1; N, 8·2%). The residue left in the Soxhlet thimble (2 g.) yielded, on treatment with silver oxide, hexahydro*apo*conessine (0·65 g.) and more of the *N*-cyano-derivative (0·37 g.), m. p. 146—147°.

N-*Demethylhexahydro*apo*conessine* (III; R = NHMe).—A solution of the *N*-cyano-derivative (III; R = NMe·CN) (4 g.) in ethanol (160 c.c.) and concentrated hydrochloric acid (120 c.c.) was refluxed for 36 hours with intermittent removal of precipitated hydrochloride. The solution was then evaporated to dryness *in vacuo*, and the residue and combined precipitates were extracted with five 100-c.c. portions of boiling ether. Evaporation of the ether left a neutral residue (0·2 g.). The hydrochloride (4 g.) was decomposed with ammonia, and the *base*, isolated with ether, was recrystallised from ethanol, giving colourless needles (2·7 g.), m. p. 80—81° (Found: C, 83·6; H, 12·1; N, 4·1. $C_{22}H_{39}N$ requires C, 83·3; H, 12·3; N, 4·4%). The N-*acetyl* derivative (III; R = NMeAc) separated from light petroleum (b. p. 90—120°)

* Thus 3-methyl-A-norcholest-3(5)-ene (Schmidt and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582; Shoppee and Summers, *J.*, 1952, 2528) has $[M]_D$ 109° more positive than cholestane. The difficulty of hydrogenating *neo*conessine and the infra-red spectrum of the base suggest the presence of a tetra-substituted ethylene linkage.

in colourless needles, m. p. 123° (Found : C, 80·3; H, 11·6; N, 3·9. $C_{24}H_{41}ON$ requires C, 80·2; H, 11·4; N, 3·9%). The *N-nitroso*-derivative (III; R = NMe·NO) separated from ethanol in colourless needles, m. p. 131° (Found : C, 76·5; H, 10·7; N, 8·4. $C_{22}H_{38}ON_2$ requires C, 76·3; H, 11·0; N, 8·1%). The *N-benzoyl* derivative (III; R = NMeBz), prepared in pyridine, formed needles (from ethanol), m. p. 161° (Found : C, 82·4; H, 9·9; N, 3·1. $C_{29}H_{43}ON$ requires C, 82·7; H, 10·2; N, 3·3%). This benzoyl derivative (36 mg.) was unaffected by refluxing its solution in ethanol (2 c.c.) and hydrochloric acid (2 c.c.) for 20 hours. Treatment with concentrated hydrochloric acid at 140° for 18 hours in a sealed tube gave, however, a good yield of the secondary base, m. p. 81°.

*Methylation of N-Demethylhexahydro*apo*conessine.*—The secondary amine (III; R = NHMe) (30 mg.) was heated with water (1 c.c.), 90% formic acid (0·5 c.c.), and 33% formaldehyde (0·5 c.c.) on the steam-bath for 4 hours; the mixture was then treated with concentrated hydrochloric acid (1 c.c.), evaporated to 0·5 c.c. under reduced pressure, diluted with water, washed with ether, and made alkaline, and the base extracted with ether. The ethereal extract was washed and evaporated, and the residue (29 mg.) recrystallised from ethanol, giving colourless needles, m. p. 67°, undepressed on admixture with hexahydro*apo*conessine of the same m. p.

*N-Chloro-N-demethylhexahydro*apo*conessine* (III; R = NClMe).—A solution of *N*-demethylhexahydro*apo*conessine (III; R = NHMe) (0·39 g.) in dry ether (50 c.c.) was treated with ethereal hypochlorous acid (0·11 g./c.c.; 25 c.c.) and kept for 2 hours in the dark at −5°. The ethereal solution was then washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, and evaporated to dryness, and the residue dried (P_2O_5) *in vacuo* and recrystallised from dry ethanol yielding colourless, prismatic needles (0·33 g.), m. p. 99—100° (Found : C, 75·1; H, 10·7; N, 3·6; Cl, 10·2. $C_{22}H_{38}NCl$ requires C, 75·1; H, 10·8; N, 4·0; Cl, 10·1%). An ethereal solution of this *chloramine* liberated iodine when shaken with acidified aqueous potassium iodide.

The chloramine (0·33 g.) in dry ethanol (10 c.c.) was treated with a solution of sodium ethoxide [from sodium (0·5 g.) and dry ethanol (20 c.c.)], and the mixture refluxed for 30 minutes with exclusion of moisture, and then evaporated to dryness. The residue was treated with ether and water; the aqueous solution on titration with silver nitrate solution (0·0197N) required 42·6 c.c. (Calc. for 1 mol. of NaCl : 47·6 c.c.). The residue (0·307 g.) from the ethereal extract was separated into a basic oil (0·275 g.) giving a neutral amorphous nitroso-derivative (Found : N, 6·0%), and a neutral oil (16 mg.), which was refluxed with ethanol (1 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for 30 minutes, yielding a non-crystalline product (12 mg.) which did not react with 2 : 4-dinitrophenylhydrazine.

Treatment of the chloramine (0·75 g.) with dry pyridine (100 c.c.) at the b. p. for 5 hours gave a base (0·56 g.), essentially *N*-demethylhexahydro*apo*conessine, m. p. 79—80°, after chromatography on alumina, and a neutral oil (92 mg.) which after hydrolysis with concentrated hydrochloric acid for 5 hours at the b. p. yielded a non-crystalline product which did not exhibit ketonic reactivity.

*Reaction of N-Benzoyl-N-demethylhexahydro*apo*conessine with Phosphorus Pentachloride.*—The benzoyl derivative (III; R = NMeBz) (1·15 g.) and phosphorus pentachloride (0·67 g.) were heated together at 180° for 8 hours, and the product, isolated with ether, was heated with concentrated hydrochloric acid (10 c.c.) at 140° for 20 hours. The mixture was diluted with water and extracted with ether; the ethereal extract yielded a neutral residue (0·36 g.), and from the acidic solution was obtained a base (0·44 g.). The basic fraction was chromatographed in light petroleum (b. p. 40—60°) on alumina (10 g.), the column being developed successively with benzene–light petroleum (b. p. 40—60°), benzene, ether–benzene, ether, and acetone. There were thus obtained some *N*-demethylhexahydro*apo*conessine and the crude *amino*allo*pregnane* (III; R = NH_2) (0·21 g.) which after crystallisation from acetone gave colourless needles (0·17 g.), m. p. 98°, raised on further crystallisation to 99—100° (Found : C, 83·9; H, 11·8; N, 4·1. $C_{21}H_{37}N$ requires C, 83·2; H, 12·2; N, 4·6%), depressed to 65° on admixture with *N*-demethylhexahydro*apo*conessine (III; R = NH_2), m. p. 80—81°. The amine (III; R = NH_2) evolved 1·8 mols. of methane on treatment with excess of methylmagnesium iodide for 1 hour at 100°. The *acetyl* derivative separated from acetone–light petroleum (b. p. 60—80°) in colourless needles, m. p. 171° (Found : C, 80·0; H, 11·2; N, 4·0. $C_{23}H_{39}ON$ requires C, 80·0; H, 11·3; N, 4·1%).

The neutral oil, after further heating with concentrated hydrochloric acid, and chromatography, gave a non-crystalline product (Found : N, 1·1; Cl, 2·9%).

Methylation of (III; R = NH_2).—The primary base (III; R = NH_2) (12 mg.) was methylated by heating it on the water-bath for 3 hours with formic acid (0·5 c.c. of 90%), water

(1 c.c.), and formaldehyde (0·5 c.c. of 33%). Concentrated hydrochloric acid (1 c.c.) was then added, and the solution concentrated to 0·5 c.c., diluted with water, washed with ether, basified with ammonia, and extracted again with ether. The product (11 mg.) separated from ethanol in fine needles, m. p. 67°, undepressed on admixture with hexahydro*apo*conessine.

Action of Nitrous Acid on (III; R = NH_2).—The amine (III; R = NH_2) (45 mg.) in ether (5 c.c.) was treated at −5° with 2N-hydrochloric acid (5 c.c.) and sodium nitrite (0·2 g.) in water (2 c.c.). After an hour's shaking all the precipitated hydrochloride had disappeared. The ethereal solution was separated, washed with dilute sodium hydroxide solution and water, and evaporated, leaving a colourless oil (43 mg.), not entirely free from nitrogen, from which no crystalline product could be obtained by chromatography. Oxidation of the oil (69 mg.) with chromium trioxide (35 mg.) in acetic acid–light petroleum (b. p. 40—60°) at 0° for 16 hours, and treatment of the non-acidic reaction product (68 mg.) with Girard-T reagent, gave a ketonic (28 mg.) and a non-ketonic fraction (40 mg.). The former after chromatography on alumina gave a colourless nitrogen-free solid (12 mg.) which crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 251—254°. No crystalline product could be obtained from the non-ketonic fraction.

Cyclisation of apo*Conessine*.—(a) *In aqueous glycol in the presence of potassium hydroxide.* A mixture of *apo*conessine (0·5 g.), ethylene glycol (60 c.c.), potassium hydroxide (12 g.), potassium iodide (2 g.), and water (8 c.c.) was concentrated slightly until the temperature of the boiling liquid was 150°, heated under reflux for 6 hours, cooled, diluted with water, and extracted successively with ether and chloroform. The extracts yielded respectively a non-crystalline basic fraction (0·2 g.) and a methiodide (0·15 g.). The basic fraction was refluxed in glacial acetic acid (5 c.c.) for 1 hour, concentrated, diluted with water, basified, and extracted with ether. The extract yielded an oily base (0·14 g.) unaffected by further treatment with acetic acid; addition of potassium iodide to the aqueous alkaline solution gave a precipitate of cyclised methiodide (0·06 g.).

The methiodide (0·15 g.) from the above chloroform extract was recrystallised twice from water, yielding colourless, rectangular plates with characteristic edge irregularities, $[\alpha]_D$ −25° (in MeOH, *c* 1·2), m. p. 318° (decomp.) (Found: C, 60·9; H, 7·8; N, 3·2; I, 28·1. Calc. for $C_{22}H_{33}N{\cdot}CH_3I$: C, 60·9; H, 7·9; N, 3·1; I, 28·0%). Samples of much lower m. p. (290°), $[\alpha]_D$ −34° (in MeOH, *c* 0·8), were obtained from the mother-liquors. The monomethiodide, $C_{22}H_{33}N,CH_3I$, obtained from conessine dimethiodide by treatment with potassium hydroxide in aqueous glycol (Part II, *loc. cit.*) and the monomethiodide obtained by cyclisation of *apo*conessine in acetic acid (Part III, *loc. cit.*) were found on repeated recrystallisation from water to form colourless plates with similar edge irregularities and had m. p. 316°, $[\alpha]_D$ −24° (in MeOH, *c* 1·0), and m. p. 308°, $[\alpha]_D$ −24° (in MeOH, *c* 1·0), respectively, the m. p.s being determined under standard conditions. No depression in m. p. was observed on admixture of any pair of these monomethiodides.

(b) *In aqueous ethylene glycol.* A solution of *apo*conessine (0·5 g.) in warm glycol (50 c.c.) was heated under reflux, and water added dropwise until the temperature of the boiling liquid was 150°. The solution was then refluxed for 2 hours, cooled, diluted with water, and basified with potassium hydroxide, and potassium iodide (2 g.) added. Extraction successively with ether and chloroform gave respectively an oily base (0·1 g.) which was not examined further, and a monomethiodide (0·4 g.). After one crystallisation from water the methiodide had m. p. 298—302°, and after a second crystallisation characteristic, irregular, rectangular plates, m. p. 318°, were obtained, unchanged on further purification, $[\alpha]_D$ −28° (in MeOH, *c* 0·9) (Found: C, 61·5; H, 8·1; N, 3·3. Calc. for $C_{22}H_{33}N,CH_3I$: C, 60·9; H, 7·9; N, 3·1%). The mother-liquors yielded a fraction, m. p. 280—290°, which was converted into methohydroxide in the usual way, and the product heated to 200° (bath-temp.)/0·1 mm. The oily distillate solidified when scratched, and after one crystallisation from methanol, colourless needles of *apo*conessine were obtained, m. p. 69°, undepressed on admixture with an authentic specimen.

(c) *In aqueous ethanol.* A solution of *apo*conessine (0·3 g.) in 90% aqueous ethanol (10 c.c.) was heated in an autoclave at 150° for 4 hours. After cooling, the solution was basified with aqueous potassium hydroxide, potassium iodide (1·5 g.) added, and the mixture concentrated to a low bulk. The residue was extracted successively with ether and chloroform; the extracts yielded respectively an oily base (0·24 g.) and a monomethiodide (0·07 g.). The monomethiodide separated from water in characteristic irregular rectangular prisms, $[\alpha]_D$ −26° (in MeOH, *c* 0·8), m. p. 315° (Found: C, 60·7; H, 7·7; N, 3·2. Calc. for $C_{22}H_{33}N,CH_3I$: C, 60·9; H, 7·9; N, 3·1%). The oily base was subjected to Hofmann decomposition in the usual way, and yielded *apo*conessine, m. p. 67—68°.

Attempted Hofmann Decomposition of apo*Conessine*.—*apo*Conessine methiodide (350 mg.) was converted in the usual way into the methohydroxide, which was decomposed at 160—200°/10 mm. The base was taken up in light petroleum (b. p. 40—60°), and hydrochloric acid (5N) added until no further precipitation occurred. The light petroleum extract yielded a colourless oil (0·75 mg.), and the bases (150 mg.) recovered from the hydrochloride were dissolved in light petroleum (b. p. 40—45°) and chromatographed on alumina (Spence's Type H, 4·5 g.). Elution with light petroleum (b. p. 40—45°) gave fractions : (*a*) colourless oil (50 mg.); (*b*) crystalline solid (40 mg.), m. p. *ca.* 80°; (*c*) yellow oil (45 mg.). Crystallisation of fraction (*b*) from methyl alcohol gave a *compound* as colourless needles (14 mg.), m. p. 93—94° (Found : C, 84·1; H, 11·0; N, 5·0. $C_{22}H_{33}N$ requires C, 84·8; H, 10·7; N, 4·5%), which were not cyclised by boiling acetic acid in the usual way.

*Attempted Hofmann Decomposition of Hexahydro*apo*conessine*.—Hexahydro*apo*conessine (Part II, *loc. cit.*) (1·1 g.) was converted *via* the methiodide in the usual way into an aqueous solution of the methohydroxide, the solution was evaporated, and the residue heated to 160° (bath temp.)/0·1 mm. for 30 minutes, a portion distilling. Residue and distillate were extracted with light petroleum (b. p. 40—60°), and the extracted product gave hexahydro*apo*conessine (746 mg., 98%) as colourless needles, m. p. 66—67° (without recrystallisation), undepressed on admixture with an authentic specimen (m. p. 67—68°), and a non-basic fraction (7 mg.) from which no crystalline product could be isolated.

Preparation of hetero*Conessine from Conessine Dimethiodide* (cf. Part II, *loc. cit.*).—A mixture of conessine dimethiodide (4 g.), ethylene glycol (300 c.c.), potassium hydroxide (60 g.), and water (50 c.c.) was concentrated until the temperature of the boiling liquid was 160°, and refluxed for 6 hours. Water (1 l.) was then added, and the bases (2 g.) were isolated with ether and refluxed in glacial acetic acid (50 c.c.) for 1 hour to remove *apo*conessine (Part II, *loc. cit.*) and conessimethine (see below). The acetic acid was removed *in vacuo*, and the residue treated with ether and aqueous ammonia. The basic residue from the ether was separated by treatment with dilute sulphuric acid into a fraction A (1·6 g.) (with sulphates soluble in cold dilute sulphuric acid) and a fraction B (0·27 g.) (with sulphates insoluble in cold dilute sulphuric acid). Fraction A on repeated recrystallisation from acetone gave *hetero*conessine (0·35 g.), m. p. 130·5—131°; a small quantity of conessine, m. p. 124°, was obtained from the mother-liquors. Fraction B, which was partly crystalline after several weeks, could not be purified by recrystallisation or chromatography.

apo*Conessine from* hetero*Conessine*.—hetero*Conessine dimethiodide* separated from water in colourless, prismatic needles, $[\alpha]_D$ +13° (in MeOH, *c* 1·0), m. p. 312° (decomp.) (Found : N, 4·1; I, 39·7. $C_{24}H_{40}N_2,2CH_3I$ requires N, 4·4; I, 39·7%). This salt (200 mg.) was converted in the usual way into an aqueous solution of the corresponding methohydroxide, which was evaporated *in vacuo*, and the residue heated to 240° (bath-temp.)/0·05 mm. The distillate (60 mg.) on crystallisation from methanol gave colourless needles of *apo*conessine, m. p. 69—70°, undepressed on admixture with an authentic specimen.

apo*Conessine from Fraction B* (*above*).—The collected oily bases (0·82 g.) from several experiments were converted into the methiodide (1·2 g.) in the usual way, and the corresponding methohydroxide was heated at 200° (bath-temp.)/0·08 mm. *apo*Conessine, m. p. 68—69°, was obtained from the distillate.

Preparation of hetero*Conessine from its Dimethiodide*.—The dimethiodide (500 mg.) was treated with potassium hydroxide in boiling aqueous glycol as described above for conessine dimethiodide. *hetero*Conessine, m. p. 131—132° (50 mg.), was obtained along with further fractions (35 mg.) melting a few degrees lower. An oily base (15 mg.) corresponding to Fraction B (above) was also obtained but was not examined further.

*Dioxy*hetero*conessine*.—A solution of *hetero*conessine (201 mg.) in sulphuric acid (2N; 3·3 c.c.) was boiled with potassium iodate (197 mg.) for a few minutes until most of the iodine had been volatilised. The pale yellow solution was basified with ammonia, and the precipitated base (220 mg.) collected and crystallised from methanol–acetone, giving *dioxy*hetero*conessine* as colourless prisms, m. p. 260° (Found : C, 74·1; H, 10·5. $C_{24}H_{42}O_2N_2$ requires C, 73·8; H, 10·8%). A fraction of m. p. 250° (Found : C, 65·7; H, 10·3%) was obtained from the mother-liquors.

Preparation of 5 : 6-*Dihydroconessimethine* (*Dihydroconessine Methine*) (IV; R = $CH{:}CH_2$) *and Tetrahydroconessimethine* (IV; R = Et).—(a) *From dihydroconessine dimethiodide*. The dimethiodide, m. p. 302—304° (decomp.), $[\alpha]_D$ +26° (in MeOH, *c* 2·0) (2 g.), was submitted to Hofmann decomposition essentially as described in Part II (*loc. cit.*), but the crude basic distillate (0·72 g.) was treated with 2N-sulphuric acid (10 c.c.) instead of concentrated hydro-

chloric acid, and thus separated into fractions A and B (with sulphates respectively soluble and insoluble in cold dilute sulphuric acid). The Hofmann decomposition was repeated twice with dihydroconessine dimethiodide (2 g. and 2·8 g.), and the combined fractions A (1·6 g.) were recrystallised from aqueous acetone to give 5 : 6-dihydroconessimethine, m. p. 64—66° (0·9 g.), together with a second crop (0·3 g.), m. p. 62—65°.

The combined fractions B were crystallised from acetone, yielding a monoacid *base* $C_{23}H_{37}N$,* which may be formulated as 5 : 6-dihydro*apo*conessine or an isomer (V) (95 mg.), $[\alpha]_D$ +64° (in $CHCl_3$, *c* 1·2), m. p. 76° (Found : C, 83·7; H, 11·1; N, 4·7. $C_{23}H_{37}N$ requires C, 84·4; H, 11·4; N, 4·3%). When this base (28·7 mg.) was hydrogenated in alcoholic solution at 20° and 732 mm. in the presence of Adams's platinum oxide catalyst (2 mg.; pre-hydrogenated) 4·6 c.c. of hydrogen were taken up in 55 minutes (calc. for two double bonds : 4·4 c.c.). The hydrogenation mixture was worked up in the usual way, and colourless needles of hexahydro*apo*conessine, m. p. 66—66·5°, were obtained, undepressed on admixture with an authentic specimen. By interrupting the hydrogenation after one mol. of hydrogen had been taken up, a base, m. p. 59—60°, was obtained, which was unaffected by boiling glacial acetic acid, indicating that the 20 : 21-double bond had undergone preferential hydrogenation.

Catalytic reduction of 5 : 6-dihydroconessimethine by the method described in Part III (*loc. cit.*) gave tetrahydroconessimethine (the " dihydromethine " of Part III), m. p. 87—89°.

(b) *From dihydro*hetero*conessine dimethiodide.* Dihydro*hetero*conessine, m. p. 104—105°, was converted in the usual way into the *dimethiodide*, which separated from methanol in colourless prisms, $[\alpha]_D$ +31° (in MeOH, *c* 2·0), m. p. 320—322° (decomp.) (Found : C, 48·6; H, 7·5. $C_{24}H_{42}N_2,2CH_3I$ requires C, 49·2; H, 7·5%). The mixed m. p. with dihydroconessine dimethiodide (m. p. 302—304°, decomp.) was 312—314°. Dihydro*hetero*conessine dimethiodide (0·77 g.) was subjected to Hofmann decomposition in the manner described above and yielded 5 : 6-dihydroconessimethine (210 mg.), m. p. 61—64° (Found : N, 7·7. Calc. for $C_{25}H_{44}N_2$: N, 7·5%), undepressed on admixture with the base prepared from dihydroconessine dimethiodide. A very small quantity of base with an insoluble sulphate (corresponding to Fraction B above) was also obtained. Catalytic hydrogenation of the dihydroconessimethine gave tetrahydroconessimethine, m. p. 88° (Found : C, 79·9; H, 12·2. Calc. for $C_{25}H_{46}N_2$: C, 80·2; H, 12·4%) undepressed on admixture with the base, m. p. 87—89°, prepared as described above.

Preparation of Conessimethine (VI).—(a) *From conessine dimethiodide* (cf. Part II, *loc. cit.*). A mixture of conessine dimethiodide (4 g.), ethylene glycol (60 c.c.), and potassium hydroxide (12 g.) was boiled for 5 minutes (internal temp. 180°), cooled, diluted with water, and extracted with chloroform, and the residue (2·5 g.) from the chloroform separated into a basic oil (1 g.) soluble in ether and the monomethiodide (1·5 g.), insoluble in ether, already described in Part II (*loc. cit.*). The basic oil was freed from *apo*conessine *via* the insoluble sulphate, and the residual base (0·81 g.), previously obtained as an oil, crystallised slowly during 6 months. The base (0·81 g.) was chromatographed in benzene on alumina (Spence's Type H; 20 g.); elution with benzene followed by ether gave a fraction (*a*) (385 mg.), m. p. 74°, fraction (*b*) (100 mg.), m. p. 90—100°, and other oily or semi-crystalline fractions. Crystallisation of (*a*) from acetone gave colourless needles of conessimethine, $[\alpha]_D$ −25° (in $CHCl_3$, *c* 1·4), m. p. 78—79° (Found : C, 81·0; H, 11·0; N, 7·5. Calc. for $C_{25}H_{42}N_2$: C, 81·1; H, 11·3; N, 7·6%) undepressed on admixture with the product, m. p. 77—78°, obtained from *iso*conessimine (Part IV, *loc. cit.*). A small yield of *hetero*conessine, m. p. 132°, was obtained by repeated crystallisation of fraction (*b*) from acetone.

(b) *From* hetero*conessine dimethiodide.* Decomposition of this dimethiodide as described above gave very similar yields of conessimethine, m. p. 77—78°, and a small quantity of *hetero*-conessine.

Cyclisation of 5 : 6-*Dihydroconessimethine* (IV; R = $CH{:}CH_2$).—(a) *In glacial acetic acid.* This reaction was carried out as described in Part III (*loc. cit.*) for " the unsaturated methine, $C_{25}H_{44}N_2$." After treatment of the cyclised product with potassium iodide and methylation of the cyclised monomethiodide with methyl iodide, the resulting dimethiodide † separated from

* In the formation of this monoacid base from dihydroconessine, the dimethylamino-group undergoes Hofmann elimination, and the low yield may be contrasted with the high yield of *apo*conessine obtained by Hofmann decomposition of conessine dimethohydroxide, where the 5 : 6-double bond activates the elimination reaction. The yield of monoacid base from dihydroconessine is of the order expected from a 3β-(equatorial) dimethylamino*allo*pregnane (cf. Parts IV and V).

† Although in Part III (*loc. cit.*) this dimethiodide was stated to be identical with dihydroconessine dimethiodide, it now seems more probable that the product is a mixture of dihydroconessine and dihydro*hetero*conessine dimethiodides.

water in colourless needles, $[\alpha]_D$ +26° (in MeOH, *c* 2·0), m. p. 310—312° (Found: C, 48·4; H, 7·5. Calc. for $C_{24}H_{42}N_2.2CH_3I$: C, 48·6; H, 7·5%). The mixed m. p. with dihydroconessine dimethiodide (m. p. 302—304°) was 310°; with dihydro*hetero*conessine dimethiodide (m. p. 320—321°) the mixed m. p. was 314°.

(b) *In aqueous glycol in the presence of potassium hydroxide.* A mixture of 5:6-dihydroconessimethine (0·5 g.), ethylene glycol (60 c.c.), potassium hydroxide (12 g.), potassium iodide (2 g.), and water (8 c.c.) was concentrated until the temperature of the boiling liquid was 150°, refluxed for 6 hours, cooled, diluted with water, and extracted successively with ether and chloroform. The basic oil from the ethereal extract was refluxed with glacial acetic acid (5 c.c.), and the base (380 mg.), which was not cyclised by this treatment, was recovered in the usual way and crystallised several times from acetone, giving dihydro*hetero*conessine as colourless needles, m. p. 102—103° (Found: C, 79·9; H, 11·8. Calc. for $C_{24}H_{42}N_2$: C, 80·4; H, 11·8%) undepressed on admixture with an authentic specimen. The chloroform extract (above) yielded a methiodide (30 mg.), which was not examined further.

(c) *In 90% aqueous alcohol.* A solution of 5:6-dihydroconessimethine (300 mg.) in 90% aqueous alcohol (10 c.c.) was heated in an autoclave at 150° for 6 hours, and cooled, and an aqueous solution containing potassium iodide (2 g.) added. The solvents were removed under reduced pressure, and the residue was extracted successively with ether and chloroform, yielding respectively a basic mixture (240 mg.) and a methiodide (100 mg.); the latter was not examined further. The basic mixture was refluxed with acetic acid (5 c.c.) for 1 hour, and the recovered bases (170 mg.) were chromatographed in light petroleum (b. p. 40—60°) on alumina (Spence's Type H; 4·5 g.); light petroleum (b. p. 40—60°), benzene, and ether were employed successively for elution. Several oily fractions were obtained, followed by a crystalline fraction (72 mg.) which on recrystallisation from acetone gave colourless needles of dihydro*hetero*conessine, m. p. 103—104°, undepressed on admixture with an authentic specimen.

Cyclisation of Conessimethine (VI) *in Aqueous Ethylene Glycol in the Presence of Potassium Hydroxide.*—A mixture of conessimethine (190 mg.), glycol (24 c.c.), potassium hydroxide (5 g.), potassium iodide (1 g.), and water (3 c.c.) was treated as in (b) above, yielding a basic oil (170 mg.) and a monomethiodide (3 mg.), which was not examined further. The basic oil was dissolved in acetic acid (3 c.c.), and the solution refluxed for 1 hour. The recovered base (120 mg.) on crystallisation from acetone gave prismatic needles of *hetero*conessine, m. p. 131—132°, undepressed on admixture with an authentic specimen.

Isolation of Conessine and Tetramethylholarrhimine.—The following modification of the extraction procedure described in Part I (*loc. cit.*) has proved very successful. A mixture of crushed seeds or bark of *Holarrhena antidysenterica* and half the weight of quicklime was extracted with ethanol (Soxhlet) for 3 days. The solvent was removed *in vacuo*, and the warm fatty residue exhaustively extracted by shaking it with 3N-hydrochloric acid. The acid extract was washed once with ether, then basified with ammonia, and the bases were extracted by shaking the whole five times with ether. The extracts were evaporated, and the basic residue was methylated with formaldehyde and formic acid as described in Part I (*loc. cit.*). The methylated basic mixture was distilled at 0·01 mm. (bath-temp., 250°), and the distillate triturated with light petroleum (b. p. 40—60°) in the proportion 100 g. of bases per l. of solvent. After 24 hours at 5°, the insoluble crude tetramethylholarrhimine was filtered off (yield variable: up to 0·03%). Evaporation of the filtrate gave crude conessine, which had m. p. 122—123° after recrystallisation from acetone. The yield of conessine was 0·4% from bark, and 0·7% from seeds.

Purification of crude tetramethylholarrhimine. The crude base as obtained above was benzoylated by the Schotten–Baumann procedure, and the crude product recrystallised several times from ethanol, yielding colourless needles of benzoyltetramethylholarrhimine, $[\alpha]_D$ −16° (in $CHCl_3$, *c* 2·5), m. p. 174—175°. Siddiqui (*loc. cit.*) gives m. p. 176°. Hydrolysis of the benzoyl derivative with aqueous-methanolic potassium hydroxide and crystallisation of the product from ethanol gave tetramethylholarrhimine as colourless needles, $[\alpha]_D$ −32° (in $CHCl_3$, *c* 2·1), m. p. 227—228° (Found: C, 77·6; H, 10·9; N, 7·1. Calc. for $C_{25}H_{44}ON_2$: C, 77·3; H, 10·4; N, 7·2%). Siddiqui (*loc. cit.*) gives $[\alpha]_D$ −45·5° (in EtOH, *c* 1), m. p. 233—235°.

Hofmann Degradation of Tetramethylholarrhimine.—Tetramethylholarrhimine (102 mg.) was converted in the usual way *via* the methiodide into an aqueous solution of the methohydroxide; the solution was evaporated, and the residue heated to 170° (bath-temp.)/0·1 mm. for 30 minutes. The white sublimate (74 mg.) was dissolved in ether, dry hydrogen chloride passed through the solution, and a precipitate (1 mg.) collected. The product (73 mg.), m. p. 94°, recovered from the filtrate was crystallised from aqueous acetone, and the cyclic *ether* thus

obtained as colourless plates, $[\alpha]_D$ −139° (in $CHCl_3$, *c* 1·5), m. p. 95—96° (Found: C, 84·1; H, 9·6; N, nil. $C_{21}H_{30}O$ requires C, 84·5; H, 10·1%). Light absorption in ethanol: $\lambda_{max.}$ 2270, 2350, 2430 Å (log ε, 4·3, 4·35, 4·1). The compound contained no active hydrogen.

Reduction of the Cyclic Ether, $C_{21}H_{30}O$.—A solution of this ether (158 mg.) in glacial acetic acid (7 c.c.) was shaken in a hydrogen atmosphere at 17·5°/750 mm. in the presence of Adams's platinum oxide catalyst (23 mg.). Hydrogen uptake (30·5 c.c. Calc. for two double bonds and the catalyst: 30·4 c.c.) was complete in 2 hours. The resulting product (160 mg.; probably a mixture of stereoisomers) separated from ethanol in colourless needles, m. p. 79—99°, and did not react with benzoyl chloride, toluene-*p*-sulphonyl chloride, 2 : 4-dinitrophenylhydrazine, or Girard-T reagent under the usual experimental conditions. The product contained no active hydrogen, and gave a negative result in the Tortelli–Jaffe test, and no colour with tetranitromethane in chloroform. No selective absorption was noted in the region 2000—3000 Å. The hydrogenated product, m. p. 79—99° (160 mg.), was repeatedly chromatographed in benzene (10 c.c.) on active charcoal in the manner described in Part III (*loc. cit.*) for a mixture of pregnane and *allo*pregnane, except that benzene was used as eluant. The "tail" fractions (30 mg.), m. p. 98—99·5°, on crystallisation from aqueous ethanol gave colourless needles of the *tetrahydro-ether*, $[\alpha]_D$ +4° (in $CHCl_3$, *c* 1·6), m. p. 98—99·5° (Found: C, 82·9; H, 11·3. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%). A considerable depression in m. p. was observed on admixture with the original product, $C_{21}H_{30}O$, m. p. 95—96°. From the "head" fractions (40 mg.), m. p. 56—68°, no homogeneous compound was isolated.

Dihydrotetramethylholarrhimine.—A solution of tetramethylholarrhimine (208 mg.) in glacial acetic acid (6 c.c.) was shaken in hydrogen at 17°/760 mm. in the presence of Adams's platinum oxide catalyst (17 mg.). Hydrogen uptake (16·6 c.c. Calc. for one double bond and the catalyst: 16·7 c.c.) was complete in 12 hours. The product was refluxed with aqueous-methanolic potassium hydroxide for 2 hours, and the *dihydrotetramethylholarrhimine* crystallised from aqueous ethanol as colourless needles, $[\alpha]_D$ +11° (in $CHCl_3$, *c* 2·5), m. p. 209—210° (Found: C, 76·4; H, 11·6; N, 7·5. $C_{25}H_{46}ON_2$ requires C, 76·9; H, 11·9; N, 7·2%).

Attempted Dehydration of Dihydrotetramethylholarrhimine.—The base (52 mg.), intimately mixed with boric oxide (178 mg.), was heated at 280° for 2 minutes at atmospheric pressure, and then at the same temperature for 15 minutes at 16 mm. (cf. Prelog and Szpilfogel, *loc. cit.*). The product, isolated with light petroleum (b. p. 40—60°), was sublimed at 180° (bath-temp.)/0·1 mm. The colourless basic sublimate (32 mg.) was converted into its hydrochloride, which was crystallised from water; the recovered *base* was obtained on crystallisation from acetone as colourless needles, m. p. 127—128° (Found: C, 79·9; H, 11·7; N, 3·8. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·4; N, 4·1%). The base was unsaturated to cold permanganate, and failed to yield a 2 : 4-dinitrophenylhydrazone. Conessine, *apo*conessine, hexahydro*apo*-conessine, and 20-dimethylamino-3β-hydroxypregn-5-ene (Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 887) were recovered unchanged after similar treatment with boric oxide.

The base (24 mg.) was shaken in glacial acetic acid (2 c.c.) in hydrogen at 19°/750 mm. in the presence of Adams's platinum oxide catalyst (5 mg.). Hydrogen uptake (2·7 c.c. Calc. for one double bond and the catalyst: 2·7 c.c.) was complete in 4 hours. Sublimation of the product at 180° (bath-temp.)/0·2 mm. and crystallisation from acetone gave the dihydro-base as colourless plates, m. p. 107—108°, saturated to cold permanganate.

Our thanks are offered to the British Council for the award of a scholarship to H. Favre, to the University of Sheffield for the award of Henry Ellison Fellowships to R. G. Powell and G. H. Whitfield, and to Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of this investigation.

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226. *The Preparation and Properties of* 1-*Phenyl*-1-*phospha*-2 : 3-6 : 7-*dibenzo*cyclo*hepta*-2 : 6-*diene and its Arsenic Analogue.*

By Frederick G. Mann, Ian T. Millar, and Bryan B. Smith.

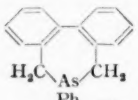
The tertiary phosphine and arsine named in the title have been prepared by the action of 2 : 2′-dilithiodibenzyl on phenyldichloro-phosphine and -arsine respectively. The compounds show isodimorphism: each exists in a low- and a high-melting form, the two low-melting and the two high-melting forms constituting isomorphous pairs.

The chemical properties, and also the absorption spectra of the above compounds and their methiodides, are discussed.

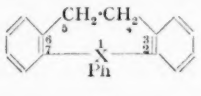
The synthesis of 6-phenyl-6-arsa-1 : 2-3 : 4-dibenzo*cyclo*hepta-1 : 3-diene (I) has recently been described by Beeby, Mann, and Turner (*J.*, 1950, 1923), who calculated that in this compound the two *o*-phenylene groups subtend an angle of *ca.* 63°: this conclusion received confirmation from the fact that the absorption spectra of the 6-phenyl and the 6-iodo-compounds were entirely free from the characteristic diphenyl band at 248 mμ, which would be shown only when these two groups approach coplanarity.

We have now prepared the isomeric 1-phenyl-1-arsa-2 : 3-6 : 7-dibenzo*cyclo*hepta-2 : 6-diene (II; X = As) and the analogous 1-phospha-derivative (II; X = P) in order to investigate their spectra: these compounds, being essentially a triaryl-arsine and -phosphine, are of course entirely different in type from (I).

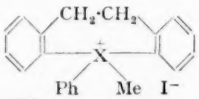
2 : 2′-Dibromodibenzyl, $Br{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4Br$, has been isolated by Beeby and Mann (*J.*, 1951, 411) as a by-product in the formation of *o*-bromobenzylmagnesium bromide, but we find that even under the most favourable conditions the yield is impractically low. For this preparation we have therefore considerably improved the method of Kenner and Wilson (*J.*, 1927, 110), whereby *o*-bromobenzyl bromide is converted by hydrazine into 1 : 1-di-*o*-bromobenzylhydrazine $(Br{\cdot}C_6H_4{\cdot}CH_2)_2N{\cdot}NH_2$, which on oxidation with mercuric oxide furnishes 2 : 2′-dibromodibenzyl.



(I)



(II)



(III)

Our attempts to convert this dibromodibenzyl into a di-Grignard reagent failed, although a variety of conditions were employed. *n*-Butyl-lithium however readily gave 2 : 2′-dilithiodibenzyl, which readily reacted with phenyldichlorophosphine to give 1-phenyl-1-phospha-2 : 3-6 : 7-dibenzo*cyclo*hepta-2 : 6-diene (II; X = P) as colourless crystals. It is of interest that this compound, when isolated from the crude reaction product by fractional distillation followed by recrystallisation, was for many weeks stable when exposed to the air at room temperature either in the solid state or in methanolic solution. When, alternatively, the crude distillate was converted into the methiodide (III; X = P) and the latter purified by recrystallisation, heating at 340°/0·001 mm. was required before dissociation of the salt gave the phosphine as a syrup, which, however, was then so susceptible to oxidation that attempted recrystallisation gave solely the phosphine oxide. It is possible that traces of iodine catalytically promote this very ready oxidation.

2 : 2′-Dilithiodibenzyl reacted similarly with phenyldichloroarsine to form the 1-arsa-compound (II; X = As) which was also isolated both by distillation and subsequent crystallisation, and by distillation followed by conversion into the methiodide (III; X = As): the latter underwent ready dissociation at 260°/0·001 mm. and the arsine thus obtained, when purified by recrystallisation, was as stable as that prepared by the first method.

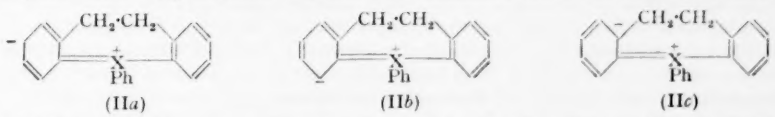
The phosphine and the arsine provide a very interesting example of the comparatively rare phenomenon of isodimorphism. These compounds, when prepared as described

above, had m. p.s 75—75·5° and 59—59·5° respectively, which were retained unchanged throughout several weeks of laboratory manipulation. A crude distilled syrupy sample of the freshly prepared phosphine solidified readily when seeded with the arsine, with which it is almost certainly isomorphous. However, in later experiments to test the stability of the heterocyclic ring, the phosphine was heated under reflux with hydriodic acid under nitrogen for 2 hours : the ring was unaffected and only an unstable hydriodide of the phosphine was isolated. This salt when hydrolysed by warm aqueous ethanol deposited however the free phosphine which after recrystallisation had m. p. 94·5—95°. When a trace of this more stable modification was either triturated with crystals of the earlier form, or added to the molten phosphine at 80°, the m. p. of the mixture rose to 94·5—95° : both forms, however, gave the same methiodide.

Furthermore, a molten sample of the arsine at 65°, when seeded with a trace of the high-melting phosphine, rapidly solidified and after recrystallisation from ethanol had m. p. 78·5—79° : this higher-melting form of the arsine could now be similarly used for the conversion of other samples of the lower-melting form. Again, both forms of the arsine gave the same methiodide. There is very little doubt therefore that each form of the phosphine is isomorphous with the corresponding form of the arsine.

It is noteworthy that the chemical stability of the phosphine towards boiling hydriodic acid is not shared by the arsine, which was converted by this treatment into dibenzyl and arsenic tri-iodide. This behaviour is similar to that of tri-*p*-methoxyphenylarsine, which Michaelis and Weitz (*Ber.*, **1887**, **20**, 48) showed was ultimately converted into anisole and arsenic tri-iodide. It is, however, in striking contrast to 2-phenyl*iso*arsindoline, 2-phenylarsaperinaphthane, 6-phenyl-6-arsa-1 : 2-3 : 4-dibenzo*cyclo*hepta-1 : 3-diene, and hexahydro-1 : 4-diphenyl-1 : 4-arsazine, in all of which the hydriodic acid treatment caused the phenyl group directly joined to the arsenic to be replaced by an iodo-group without, however, any fission of the heterocyclic ring (Mann and his co-workers, *J.*, **1947**, 662; **1950**, 1917, 1923; **1951**, 886). In these four compounds, however, the arsine is systematically a dialkylmonoarylarsine, whereas our present arsine (II; X = As) is a triarylarsine. It appears from these examples that this type of fission is limited to aryl groups directly joined to arsenic.

In view of the triaryl nature of the phosphine and arsine (II; X = P and As), considerable interest attaches to a comparison of their absorption spectra with those of their triphenyl analogues. (In both Figs. 1 and 2, the scale of $\log_{10} \varepsilon$ values for the phosphorus compounds has been raised above that of the arsenic compounds to avoid overmuch superposition of the curves.) It will be seen in Fig. 1 that the spectrum of the phosphine (II; X = P) is closely similar to that of triphenylphosphine, and that of the arsine (II; X = As) also to that of triphenylarsine, all four compounds showing only one broad absorption band. If any of these four compounds possessed three independently absorbing benzenoid rings, several absorption bands would be expected, with the main absorption at about $\lambda_{max.}$ 255 mμ, $\log_{10} \varepsilon_{max.}$ 2·8. The absence of these individual bands and the greater intensity indicate considerable resonance from the numerous forms such



(II*a*) (II*b*) (II*c*)

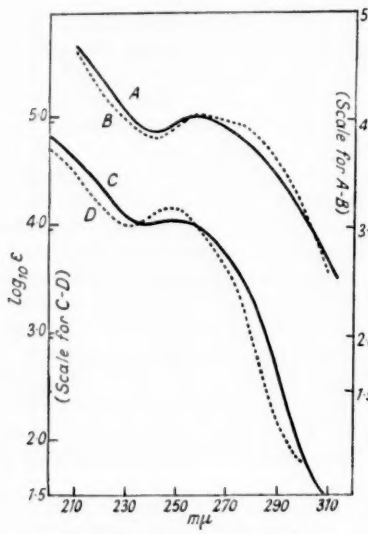
as (II*a*), (II*b*), and (II*c*), a type of resonance which clearly will be little affected by the ·CH_2·CH_2· chain joining two of the benzene rings : hence it would be expected that the members of each pair of compounds would have very similar spectra.

In Fig. 2 are shown the spectra of the methiodides of the above four compounds : in these salts the positive charges on the phosphorus and the arsenic atoms prevent resonance of the above type, and the main absorptions have now considerably lower intensities. The interesting feature is now however the very close resemblance between the spectra of the methiodides of the phosphine and arsine (II; X = P and As) and between those of the methiodides of triphenyl-phosphine and -arsine, the change of the hetero-atom having very little effect. It is probable that the several bands in the region 250—280 mμ shown

by the methiodides of triphenyl-phosphine and -arsine represent the normal absorption of the benzene groups, which are apparently merged into one main broad absorption in the heterocyclic methiodides.

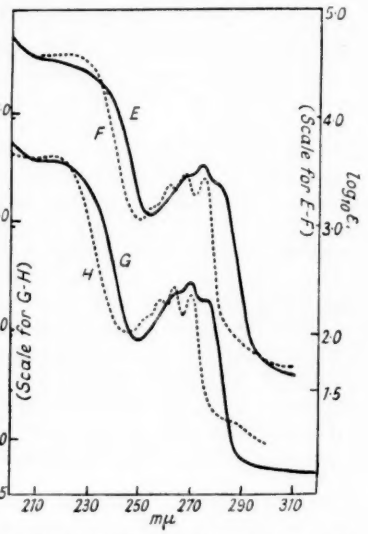
It is noteworthy that Bowden and Braude (*J.*, 1952, 1068) have shown that dimethylphenyl-phosphine and -arsine both show one broad absorption band, whereas the methiodides of these compounds show four bands between 250 and 272 mμ, which they describe as " resembling that of benzene in the 250 mμ region." The spectra of their compounds thus show a strong general resemblance to those which we have obtained for triphenyl-phosphine and -arsine and their methiodides respectively.

FIG. 1.



A, *The phosphine* (II; X = P).
B, *Triphenylphosphine*.
C, *The arsine* (II; X = As).
D, *Triphenylarsine*.

FIG. 2.



E, *Methiodide of the phosphine* (II; X = P).
F, ,, *triphenylphosphine*.
G, ,, *the arsine* (II; X = As).
H, ,, *triphenylarsine*.

EXPERIMENTAL

Consistent values for certain m. p.s could be obtained only if they were determined in evacuated tubes: these are denoted (E. T.).

2 : 2′-*Dibromodibenzyl*.—The following preparation is based on that by Kenner and Wilson (*loc. cit.*) who give very little detail of their small-scale work.

1 : 1-*Di-o-bromobenzylhydrazine hydrochloride*. A solution of *o*-bromobenzyl bromide (325 g.) in ethanol (750 c.c.) was added during 1 hour to pure hydrazine hydrate (100 g.) in ethanol (225 c.c.), with stirring and under a condenser. During the addition, hydrazine hydrobromide separated as an oil which solidified if the mixture was allowed to cool. The ethanol was then distilled, and water (1750 c.c.) added to the residue which was extracted with ether (1 l.; then 2 × 300 c.c.). The united, dried, filtered extracts were diluted with a solution of saturated ethanolic hydrogen chloride (50 c.c.) in ethanol (400 c.c.), whereby the required hydrochloride was precipitated. The latter was at once collected, and purified by dissolution in boiling ethanol (1 l.), cooling, and reprecipitation by ether (1900 c.c.). The purified product was collected, washed with ether, and dried in a vacuum (m. p. 211—212°; 91 g., 34%). The ethanolic hydrogen chloride mother-liquor when set aside deposited crude tri-*o*-bromobenzylhydrazine hydrochloride.

Oxidation. The hydrochloride (90 g.) was shaken with 5% aqueous sodium hydroxide (200 c.c.), which was then extracted with chloroform (2 × 150 c.c.). The combined extracts were dried (Na_2SO_4), and the hydrazine was oxidised by the addition of finely powdered yellow mercuric oxide (60 g.), in portions (10 g.) during 1 hour, to the vigorously stirred solution.

nitrogen being evolved. The mixture was stirred for a further 3 hours, then filtered, and the solvent evaporated. The residue, which completely solidified on cooling, could not be purified satisfactorily by recrystallisation alone. Distillation however gave the 2 : 2′-dibromodibenzyl as a fraction, b. p. 138—148°/0·013 mm., which rapidly solidified, and when recrystallised from ethanol formed colourless crystals, m. p. 83—84° (38·5 g., 51%). The crude product probably contained some di-*o*-bromobenzylmercury, because during the distillation metallic mercury was liberated.

n-*Butyl-lithium*.—This was prepared under nitrogen by the method of Gilman, Langham, and Moore (*J. Amer. Chem. Soc.*, 1940, **62**, 2327), with however light petroleum of b. p. 40—45° instead of that of b. p. 28—38°. Before use, the concentration of the reagent was determined by titration with N/10-hydrochloric acid (methyl-orange).

1-*Phenyl*-1-*phospha*-2 : 3-6 : 7-*dibenzo*cyclo*hepta*-2 : 6-*diene* (II; X = P).—This preparation was performed in a flask fitted with a sealed stirrer, reflux condenser, dropping funnel, and an inlet tube through which nitrogen passed throughout the experiment. Solutions of 2 : 2′-dibromodibenzyl (15·3 g.) in light petroleum (b. p. 40—45°; 300 c.c.) and of *n*-butyl-lithium (2·2 mols. : 112 c.c. of 0·882N-solution, also in this petroleum) were mixed, boiled under reflux for 12 hours, set aside overnight, and then chilled in ice-water whilst a solution of phenyldichlorophosphine (8·06 g., 1 mol.) in benzene (150 c.c.) was added with stirring during 30 minutes. The mixture was then boiled for 3 hours, again chilled, and hydrolysed with air-free water (200 c.c.). The organic layer was collected, dried (Na_2SO_4), and freed from solvent, and the residue distilled at 0·01 mm., giving the fractions: (*a*) b. p. 150—170° (*ca.* 5 g.); readily solidified; mainly 2 : 2′-dibromodibenzyl; (*b*) b. p. 170—190°; a pale amber syrup (4 g.) which solidified when stirred with ethanol and then seeded with the arsine, m. p. 59° (see later), and when then twice recrystallised from ethanol gave the *phosphine* as colourless crystals, m. p. 75—75·5° (3 g., 23%) (Found: C, 83·3; H, 5·8; *M*, ebullioscopic in 0·859% ethanol solution, 289. $C_{20}H_{17}P$ requires C, 83·3; H, 5·95%; *M*, 288); (*c*) b. p. 190—230°; a viscous liquid which formed a milky glass (*ca.* 4 g.). This fraction could not be crystallised and did not form a crystalline methiodide: it probably consisted mainly of a linear polymeric phosphine, contaminated with the above cyclic phosphine. The fraction was repeatedly extracted with petroleum (b. p. 60—80°) and the united extracts, when evaporated in the air, deposited a gum which on recrystallisation from ethanol gave in small yield the phosphine oxide, m. p. 173—174°, undepressed by admixture with that described below.

The phosphine (II; X = P) did not form a stable hydrochloride or a picrate.

Methiodide. The fraction (*b*) dissolved readily in methyl iodide with heat evolution and subsequent deposition of the *methiodide*, colourless crystals (from ethanol), m. p. 251—252° (E. T.) (Found: C, 58·75; H, 4·9. $C_{21}H_{20}IP$ requires C, 58·65; H, 4·7%). The thermal stability of this salt is markedly greater than that of its arsenic analogue. For example, a sample was heated in nitrogen at 300—310°/0·001 mm. for 30 minutes, and the residue when recrystallised from ethanol gave the unchanged methiodide in high yield: the ethanolic mother-liquor contained some free phosphine mixed with the unchanged methiodide, for, when boiled with an excess of potassium palladochloride, it afforded *di-iodobisphosphine-*μ*-di-iodopalladium*, chocolate-brown crystals, m. p. 283—285° (decomp.), from ethanol (Found: C, 36·75; H, 2·45. $C_{40}H_{34}I_4P_2Pd_2$ requires C, 37·0; H, 2·6%). When the methiodide was similarly heated at 340—345°, decomposition occurred, but the gummy distillate when recrystallised from methanol gave the colourless *oxide*, m. p. 173·5—174·5° (Found: C, 78·45; H, 5·45. $C_{20}H_{17}OP$ requires C, 78·9; H, 5·6%). The pure phosphine, obtained by direct crystallisation of fraction (*b*) above, was however unchanged after exposure to the air for 14 days, and its methanolic solution when similarly exposed deposited large crystals of the unchanged phosphine, m. p. 75·0—75·5° (mixed and unmixed).

An ethanolic solution of the phosphine, when boiled with aqueous potassium palladochloride, deposited the *dichlorobisphosphinepalladium*, which separated from dioxan as fine yellow crystals, m. p. 278—280°, which even after heating at 100°/0·1 mm. for 8 hours still retained dioxan of crystallisation (Found: C, 62·7; H, 4·9. $C_{40}H_{34}Cl_2P_2Pd,C_4H_8O_2$ requires C, 62·7; H, 5·0%).

Action of hydriodic acid. A mixture of the phosphine (0·1 g.) of m. p. 75—75·5° and pure hydriodic acid (30 c.c.) of constant b. p. was boiled under reflux in nitrogen for 2 hours, a clear solution being obtained without other apparent change. Evaporation under nitrogen then gave an oily residue which crystallised when cooled and scratched. These colourless crystals (which were apparently a crude hydriodide) were very soluble in water, but could not be recrystallised from any common solvent without decomposition: at room temperature they very rapidly decomposed with liberation of iodine, and when heated they melted indefinitely.

An aqueous ethanolic solution, when boiled and cooled, deposited the high-melting form of the phosphine as colourless crystals, m. p. 94·5—95° after two recrystallisations from ethanol (Found : C, 83·5 : H, 6·2%).

Within a few days of the first isolation of this form, it was found that the low-melting form, when heated in a sealed capillary tube still melted at 75—75·5°, but when heated in an open tube started to soften at 75° and then before fusion was complete started to resolidify from the top downwards, becoming completely solid at 80° and finally melting sharply at 95—95·5°.

1-*Phenyl*-1-*arsa*-2 : 3-6 : 7-*dibenzo*cyclo*hepta*-2 : 6-*diene* (II; X = As).—This was prepared precisely as the analogous phosphine, by using 2 : 2′-dibromodibenzyl (10·2 g.) in light petroleum (200 c.c.), *n*-butyl-lithium (2·2 mols., 68 c.c. of 0·97N), and phenyldichloroarsine (6·7 g., 1 mol.) in benzene (100 c.c.). After removal of the solvent, distillation at 0·15 mm. gave the fractions : (*a*) b. p. 115—155°, 0·8 g.; (*b*) b. p. 155—180°, 0·7 g.; and (*c*) b. p. 180—183°, 2·2 g. Fraction (*c*) completely crystallised, whereas (*a*) and (*b*) remained semi-solid. A portion of (*c*), when recrystallised from ethanol, gave the pure arsine (II; X = As). To conserve material, however, these fractions were dissolved together in methyl iodide, and rapidly deposited the colourless *methiodide* (III; X = As) (1·7 g.), m. p. 215—227° (E.T.) after recrystallisation from ethanol (Found : C, 52·6; H, 4·25. $C_{21}H_{20}IAs$ requires C, 53·2; H, 4·25%). The undistilled residue, when boiled with methyl iodide, gave a second crop (2·7 g.) of the methiodide. This salt is slightly soluble in hot water, readily so in cold methanol, and sparingly so in ethanol; the wide melting range was shown by several preparations and is apparently characteristic.

The methiodide (0·95 g.), when heated in nitrogen at 260°/0·001 mm., decomposed giving a pale yellow distillate which crystallised when cooled and scratched; recrystallisation from ethanol gave the colourless *arsine* (II; X = As), m. p. 59—59·5° (0·45 g., 75%) (Found : C, 72·3; H, 4·9. $C_{20}H_{17}As$ requires C, 72·3; H, 5·2%).

An acetone solution of the arsine, when treated with an excess of hydrogen peroxide, set aside overnight, and then evaporated, gave a crystalline residue, m. p. *ca.* 40°, too soluble in common solvents for recrystallisation; when dried at 75°/0·1 mm. for 18 hours, this gave the anhydrous *arsine oxide*, m. p. 188—190° (decomp.) (Found : C, 68·9; H, 5·2. $C_{20}H_{17}OAs$ requires C, 69·0; H, 4·9%).

The arsine, when treated with potassium palladochloride as described for the phosphine, gave the *dichlorobisarsinepalladium*, which crystallised from dioxan as a dark yellow microcrystalline powder, m. p. 275—277°, which after 1·5 hours at 50°/0·1 mm. still retained solvent of crystallisation (Found : C, 56·85; H, 4·3. $C_{40}H_{34}Cl_2As_2Pd,0{\cdot}5C_4H_8O_2$ requires C, 56·9; H, 4·3%).

Action of hydriodic acid. This was performed precisely as for the above phosphine, but an orange solid began to separate at once on heating. The mixture, after 2 hours' boiling, was concentrated under reduced pressure in nitrogen. The hydriodic acid distillate deposited colourless crystals of dibenzyl which were collected, washed with water, and dried : they had m. p. 52°, unchanged by admixture with an authentic sample. The residue in the flask, when collected and washed with ethanol, afforded orange-red crystals of arsenic tri-iodide, m. p. 139—140°.

Absorption Spectra.—These were all determined in ethanolic solution (see Table and Figs.).

	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$		$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
Phosphine (II; X = P)	256—257	11,200	242	7800	PPh_3MeI	220—223	39,800	210—216 †	38,700 †
						261	2,390	249—250	1200
Ph_3P	262—263	11,100	242	6900		268	3,100	263	2290
						275	2,700	271	2000
Arsine (II; X = As)	246—248	10,680	236	9920	$AsPh_3MeI$	216	41,560	205	39,670
						258	1,890	245	946
Ph_3As	248	13,340	233	9440		264	2,440	261	1730
Methiodide of (II; X = P)	275	3,550	254	1270 *		271	2,060	267	1420
Methiodide of (II; X = As)	270	2,730	249	295 *					

* Principal values only. † Inflexion.

The curve for triphenylphosphine closely resembles that of Purvis (*J.*, 1914, **105**, 1377), but that of triphenylarsine and of methyltriphenylarsonium iodide differ markedly from those given by Purvis and McCleland (*J.*, 1912, **101**, 1514) and Hantzsch (*Ber.*, 1919, **52**, 1544) respectively.

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227. *The Methanesulphonic Acid–Sulphur Trioxide Complex: Detection by Raman Spectroscopy.*

By I. Sandeman.

The Raman spectra and crystallising points of solutions of sulphur trioxide of varying concentration in methanesulphonic acid have been measured. It is concluded that a mixed anhydride of methanesulphonic and sulphuric acids is formed, and this forms the complex $Me{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH,2Me{\cdot}SO_3H$. The Raman spectrum of oleum is also reported.

Vicary and Hinshelwood (*J.*, 1939, 1372), in studying the kinetics of the sulphonation of nitrobenzene by sulphur trioxide, concluded that the reaction was of the second order with respect to the trioxide and was strongly retarded by the formation of a complex between it and the sulphonic acid. Their data indicate a 1 : 1 complex. A similar conclusion was reached by Wadsworth and Hinshelwood (*J.*, 1944, 469) in studying the kinetics of the sulphonation by sulphur trioxide of *p*-nitrotoluene and chlorobenzene. It is important for the interpretation of the kinetics of sulphonation to determine whether complexes are formed between sulphur trioxide and sulphonic acids. With this end in view, an attempt was made to study the Raman spectrum of toluene-*p*-sulphonic acid solutions in oleum. This attempt had, however, to be abandoned, because it proved impossible to obtain solutions of sufficient clarity for investigation of their spectra. Satisfactory results were, however, obtained with solutions of sulphur trioxide in methanesulphonic acid.

Pyrosulphuric acid is known from Chédin's work (*Ann. Chim.*, 1937, **8**, 243) to have a Raman spectrum entirely distinct from that of sulphuric acid, and the changes resulting from the treatment of sulphuric acid with increasing quantities of the trioxide can be followed spectroscopically. Briefly, what happens is that in oleum of low trioxide content the Raman lines of concentrated sulphuric acid are observed, but increase of trioxide causes decreasing intensity, and new lines due to pyrosulphuric acid appear. As the equimolecular stage of concentration is reached (about 45% SO_3 by wt.), the sulphuric acid spectrum fades out, and only that of pyrosulphuric acid is left. At still higher concentrations new lines traceable to free trioxide appear superimposed on the pyrosulphuric acid spectrum. If sulphonic acids form analogous compounds with sulphur trioxide, similar changes should occur in the Raman spectra of their solutions with the trioxide.

As the principal desideratum in handling the methanesulphonic acid solutions of sulphur trioxide was to minimise contact with moisture and dust-laden air, the apparatus used was designed for preparing the solutions and introducing them into the Raman tube entirely under glass. When air was rigidly excluded, the solution in the Raman tube showed only a very faint pink colour when the tube was viewed in daylight through the optical flat closing its end. The Raman tube was surrounded with a heating coil which could be used to prevent the contents from solidifying.

The Raman Spectra.—The spectrum of sulphuric acid is shown in Table 1, that of methanesulphonic acid in Table 2, and the spectra of pyrosulphuric acid and the complex formed between methanesulphonic acid and sulphur trioxide side by side in Table 3. These tables give approximate visual estimates of intensity based on the best exposures.

The Raman spectrum was taken with a Hilger E 612 spectrograph. A filter containing solutions of sodium nitrite and praseodymium nitrate was used, which served to clarify the spectrum on the long-wave side of the exciting mercury line 4358 Å as well as to reduce the intensity of the 4047 Å line. The lamp-head consisted of four Osira lamps under-run at 20—60 volts. Exposures of 14½ hours were made with a slit of about 25 μ. As the spectra studied were diffuse, it is only possible to claim an accuracy of about ±6 cm.$^{-1}$ for the Raman shifts, that of the stronger lines averaged over a considerable number of plates being better than this (cf. the measurements of sulphuric acid in Table 1 with literature values). Wave-lengths were calculated from the comparison spectrum of a small neon lamp by Hartmann interpolation.

To obtain the spectrum of pyrosulphuric acid, oleum of various weight concentrations of trioxide up to 56% was used. The results of this work confirmed those of Chédin (*loc. cit.*). and the general conclusions were the same, *viz.*, those recorded on p. 1135, but there are differences in detail. Chédin gives pyrosulphuric acid lines at the following wave-numbers : 300, 327, 480, 735, 960, and 1250 cm.$^{-1}$. The first two are components of the doublet given in Table 3 as 311 cm.$^{-1}$. The next three correspond to those at 465, 729, and 944 cm.$^{-1}$.

TABLE 1. *Raman spectrum of sulphuric acid.**

$\Delta\nu$, cm.$^{-1}$	Previous work : † A	B	$\Delta\nu$, cm.$^{-1}$	Previous work : † A	B	$\Delta\nu$, cm.$^{-1}$	Previous work : † A	B
411 (3)	410 (1b)	381	911 (5)	916 (8)	910	1136 (3)	1140 (4)	1121
Doublet		417	969 (1b) ‡		978	1187 (0)		1195
561 (4b)	564 (5b)	555	1049 (2)	1045 (0)		1365 (1b)	1364 (1)	

* b = Broad.

† A = Angus and Leckie, *J.*, 1939, 1372. B = Woodward and Horner, *Proc. Roy. Soc.*, 1934, *A*, **144**, 129.

‡ This line was difficult to measure owing to its nearness to the barium line 4554 Å, a trace of which appeared on all the plates, owing to the fact that the electrodes of Osira lamps are coated with barium oxide.

TABLE 2. *Raman spectrum of methanesulphonic acid*, $\Delta\nu$(cm.$^{-1}$).

335 (3b),* 502 (2), 535 (4), 769 (6), 895 (1), 1179 (4), 1413 (3), 2945 (5), 3030 (3), 3125 (3).

* Doublet with components about 324 and 341.

Notes : (i) b = Broad.
(ii) Besides the above there were traces of lines at 253, 292, and 980 cm.$^{-1}$.
(iii) The lines at 769 and 2945 cm.$^{-1}$ come very near lines observed in the complex with SO_3. In the case of 2945 cm.$^{-1}$ this is not surprising since CH_3 stretching vibrations would not be expected to vary very much between the sulphonic acid and its complex with SO_3.

TABLE 3. *Raman spectra of pyrosulphuric acid and of* $CH_3{\cdot}SO_3H{-}SO_3$ *complex*, $\Delta\nu$(cm.$^{-1}$).

$H_2S_2O_7$	Complex	$H_2S_2O_7$	Complex	$H_2S_2O_7$	Complex
234 (1) *	230 (1) *	498 (1)	—	810 (0)	772 (1) ‖
271 (1)	261 (2)	527 (2) ‖	513 (4)	901 (5)	922 (0)
311 (4b) †	309 (5b) ‡	682 (1)	655 (2) ‖	944 (1) *	944 (1) *
334 (1)	372 (2) ‖	729 (4) *	691 (4)	—	1177 (5)
465 (1) *	469 (1) *	798 (1)	731 (2) *	—	2945 (3)

Notes : (i) b = Broad.
(ii) A few very faint lines observed in only one plate are omitted from the lists.

* These lines occur at about the same wave-number in both complexes.
† Doublet with components about 298 and 327.
‡ Doublet with components about 301 and 317.
‖ These lines come very near those of gaseous SO_3.

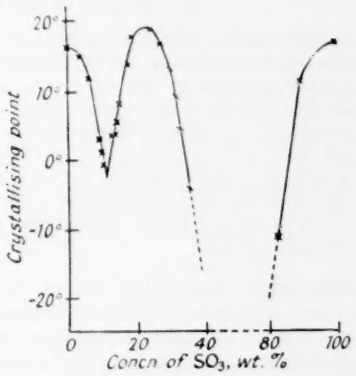
The last was not observed, unless it corresponds to the trioxide line at 1226 cm.$^{-1}$. Chédin also identified trioxide lines at 245, 535, 688, and 1075 cm.$^{-1}$. These correspond to lines found at 234, 527, 682, and 1068 cm.$^{-1}$. It seems likely that only the last is an actual line of the trioxide. Measurements of the Raman lines of gaseous trioxide are now available from the work of Gerding and Nijveld (*Rec. Trav. chim.*, 1940, **59**, 1206). It seems at this stage safest to classify as lines due to the trioxide only those which appear in its solutions in both sulphuric acid and methanesulphonic acid of high trioxide concentration at wave-numbers agreeing with the literature values for the Raman spectrum of the trioxide. When this is done, only five lines observed in the spectra of these solutions can be allocated with certainty to sulphur trioxide, *viz.*, at 123 (0), 166 (1), 1068 (6), 1226 (4, sharp), and 1390 (3, diffuse doublet). Lines found in the spectra of pyrosulphuric acid and the methanesulphonic acid–trioxide complex (but not in both) which come near the literature values for trioxide lines are indicated in Table 3.

The Raman spectrum of solutions of the trioxide in methanesulphonic acid was obtained for various weight-concentrations up to 67%. The results showed that the spectrum of the parent liquid fades with increase of trioxide and is replaced by that of the complex, just as in the case of oleum, except that the onset of the spectrum of the complex here appears

to take place at a lower concentration of trioxide. As with oleum, the lines of the trioxide begin to appear when it reaches a high concentration.

Crystallising Points of Solutions of Sulphur Trioxide in Methanesulphonic Acid.—The apparatus used consisted of a tube about 30 cm. long, in two parts joined by a cone and socket. By rotating the top part in the course of taking crystallising points it was possible to alter the position of the thermometer and so facilitate readings. The lower part of the tube was fitted with a spiral stirrer actuated by a handle in a side-arm. Cone and socket joints were lubricated with methanesulphonic acid. To decrease the rate of cooling, a cork and outer tube were fitted to interpose an air space between the solution and the cooling-bath. Crystallising points were found by slow cooling and noting the highest temperature indicated by the thermometer after solidification had set in. At points on the low-concentration side of the first eutectic, *viz.*, those for which methanesulphonic acid came out of solution on freezing, this method may yield low results since extensive supercooling was possible. The figure shows a graph of crystallising point plotted against weight-concentration of trioxide. For concentrations between 37% and 83% the liquid became very viscous and crystallising points could not be measured.

Discussion.—The Raman spectra show that a complex is formed between methanesulphonic acid and sulphur trioxide and the m. p. diagram, which has a peak about con-



Concentration of SO_3 *(by wt.) in* $Me{\cdot}SO_3H$ *solution plotted against crystallising point.*

centration 21%, shows that the compound solidifying from solution contains 3 molecules of methanesulphonic acid to one of sulphur trioxide. The configuration of such a complex would appear at first sight to be a hydrogen-bonded one, since any other configuration than this would involve the placing of too many oxygen atoms round the central sulphur atom of the trioxide molecule entering into the complex. The Raman spectrum of the complex, which differs from that of methanesulphonic acid and resembles that of pyrosulphuric acid, is, however, not easy to reconcile with a hydrogen-bonded configuration.

Vicary and Hinshelwood's data (*loc. cit.*) for the kinetic behaviour of the sulphonation of nitrobenzene have been examined and found inconsistent with the assumption of a 3 : 1 complex $3NO_2{\cdot}C_6H_4{\cdot}SO_3H,SO_3$. In considering the facts of the case one must take into account a chemical property of solutions of the trioxide in methanesulphonic acid, *viz.*, that, if a solution containing up to about 40% of trioxide is poured into water, a white precipitate is formed in small yield which appears to be methanesulphonic anhydride.

The above facts are all consistent with an initial reaction of methanesulphonic acid with sulphur trioxide to give the mixed anhydride $Me{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH$, followed by the attachment of two molecules of methanesulphonic acid by hydrogen bonding. As far as the Raman spectrum is concerned this view would explain why spectra of solutions of sulphur trioxide in methanesulphonic acid are so different from that of methanesulphonic acid and resemble that of pyrosulphuric acid. It would also explain why the spectrum of the trioxide begins to appear only at a concentration of about 50% and why some traces of the methanesulphonic acid spectrum are found at concentrations about 20%. With regard

to the crystallising-point curve, the view would explain why a peak occurs at a concentration of about 21%. (The theoretical peak concentration for $Me{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH,2Me{\cdot}SO_3H$ would be 21·7%.) The absence of a peak at 45·5% (theoretical peak concentration for $Me{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH$) would also be explained, since amounts of pure methanesulphonic acid and sulphur trioxide must be presumed present which would depress the crystallising point. The view would also be consistent with the evidence for 1 : 1 complexes in the case of aromatic sulphonic acids and would explain the formation of methanesulphonic anhydride when solutions of the trioxide in methanesulphonic acid are poured into water, since the function of the water would be to remove the hydrogen-bonded $Me{\cdot}SO_3H$ molecules, the reaction then proceeding :

$$2Me{\cdot}SO_2{\cdot}O{\cdot}SO_2{\cdot}OH + H_2O \longrightarrow (Me{\cdot}SO_2)_2O + 2H_2SO_4.$$

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228. *Quinones. Part II. The Addition of Mercapto-acids to Benzoquinones and* 1 : 4-*Naphthaquinone.*

By A. Blackhall and R. H. Thomson.

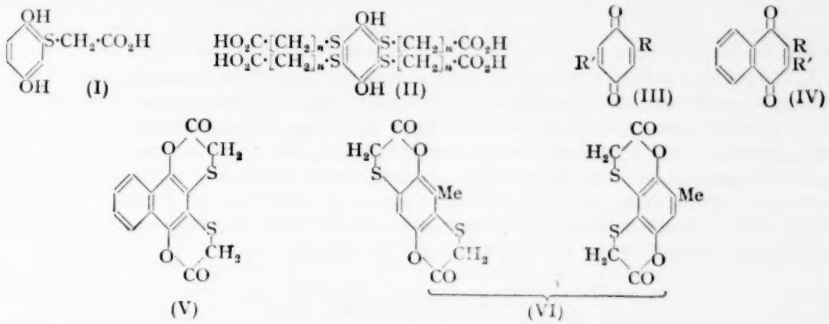
The reaction of thioglycollic acid with equimolecular amounts of benzoquinone, toluquinone, *m*- and *p*-xyloquinone, and 1 : 4-naphthaquinone in aqueous suspension has been studied. In all cases, except possibly toluquinone, all the reactive positions are attacked. β-Mercaptopropionic acid is equally reactive, yielding the quinol (II; $n = 2$) with benzoquinone, and the quinones (IV; $R = -S{\cdot}[CH_2]_2{\cdot}CO_2H$, $R' = H$, and $R = R' = -S{\cdot}[CH_2]_2{\cdot}CO_2H$) with 1 : 4-naphthaquinone. γ-Mercaptobutyric acid formed only a di-addition product with benzoquinone under the same conditions, as did propane-1-thiol. Thiophenol gave a mixture of mono- and di-phenylthiobenzoquinone.

In connection with other work, we recently attempted to prepare 2-carboxymethylthioquinol (I), by condensing 2-chlorobenzoquinone with thioglycollic (mercaptoacetic) acid. Reaction in alcohol containing pyridine gave a mixture, but in aqueous suspension at room temperature a small amount of a colourless compound, m. p. 276° (decomp.), was obtained. However this substance, which we also obtained by interaction of equimolecular amounts of benzoquinone and thioglycollic acid under the same conditions, was not (I) but 2 : 3 : 5 : 6-tetra(carboxymethylthio)quinol (II; $n = 1$), previously obtained by Schubert (*J. Amer. Chem. Soc.*, 1947, **69**, 712), who established its structure by its preparation from chloranil and thioglycollic acid. This tetra-addition product is formed rapidly in aqueous suspension at room temperature, and *ca.* 18% of the thioglycollic acid is converted into it even when added slowly to the quinone. The reaction is not inhibited by the presence of picric acid. Although the addition of thiols to quinones appears to proceed by a radical mechanism in certain cases (Thomson, *J. Org. Chem.*, 1951, **16**, 1082, and Part III, in preparation) the addition of thioglycollic acid to benzoquinone is almost certainly an ionic reaction, and proceeds by alternate addition and oxidation, four molecules of benzoquinone being required to produce one molecule of (II; $n = 1$) (Schubert, *loc. cit.*, isolated 63% of quinol).

The addition of thioglycollic acid to equimolecular quantities of toluquinone, *m*- and *p*-xyloquinones, and 1 : 4-naphthaquinone in aqueous suspension is very similar. In all cases, except possibly toluquinone, the thioglycollic acid attacks all the free reactive positions giving the corresponding quinols. Both mono- and di-addition products were isolated from the reaction with naphthaquinone. This has not been observed before in the naphthaquinone series except in the addition of methane- and ethane-thiol (Miyaki, Ikeda, and Mizuno, *J. Pharm. Soc. Jap.*, 1951, **71**, 643), where a large excess of thiol was used.

In the addition of thioglycollic acid to toluquinone the products were obtained as an oil, and attempts to obtain solid derivatives under mild conditions failed. By heating at

190°/1 mm. toluquinol was removed, and a solid residue obtained which yielded two compounds. The failure of these compounds to react with diazomethane and acetyl chloride, and their desulphurisation with Raney nickel to toluquinol diacetate, established the structures of the two substances as the isomeric dilactones (VI). Failure to isolate a tri-addition product from the reaction mixture does not exclude its formation, since it was formed by interaction of trichlorotoluquinone and thioglycollic acid, and was found to be



extremely soluble in water and very difficult to extract with ether. It was necessary to make the aqueous solution strongly acid, and ether extraction then afforded the monolactone. We were not able to isolate the tricarboxylic acid. The addition of thioglycollic acid to toluquinone in benzene solution gave a dark red oil, which could not be purified.

The crude product arising from reaction of thioglycollic acid with 1 : 4-naphthaquinone could not be purified, because of its sensitivity to aerial oxidation, but oxidation with chromic acid yielded a mixture of quinones, from which only 2-carboxymethylthio-1 : 4-naphthaquinone (IV; R = S·CH_2·CO_2H, R′ = H) could be isolated. Its structure was established by replacement of the carboxymethylthio-group by aniline, to give 2-anilino-1 : 4-naphthaquinone. With acetic anhydride the crude quinol mixture afforded the dilactone (V), which was also prepared from the quinol obtained by reaction of 2 : 3-dibromo-1 : 4-naphthaquinone and thioglycollic acid.

The remarkable reactivity of thioglycollic acid has been noted previously by Fieser and Turner (*J. Amer. Chem. Soc.*, 1947, **69**, 2335) who found that, in contrast to most other addition reagents, it reacted readily with 2-methyl-1 : 4-naphthaquinone. In the case of 2-*tert.*-butyl-1 : 4-naphthaquinone, however, steric hindrance is too great and we could detect no reaction after 12 hours' refluxing in alcohol or 28 days' storage at room temperature. Attempts to add thioglycollic acid to dibenzylideneacetone also failed.

The reaction of thioglycollic acid with benzoquinone is not unique. Under the same conditions (*i.e.*, using equimolecular amounts) β-mercaptopropionic acid also gives rise to a tetra-addition product (II; $n = 2$), and with 1 : 4-naphthaquinone mono- and di-addition products were again obtained. Oxidation of the last two gave (IV; R = S·$[CH_2]_2$·CO_2H, R′ = H, and R = R′ = S·$[CH_2]_2$·CO_2H respectively). Addition of γ-mercaptobutyric acid to benzoquinone however yielded only a 2 : 5(?)-disubstituted quinone (III; R = R′ = S·$[CH_2]_3$·CO_2H), and 2 : 3 : 5 : 6-tetra-(3-carboxypropylthio)-quinol (II; $n = 3$) (prepared from chloranil) was not found. (III; R = R′ = S·$[CH_2]_3$·CO_2H) could not be obtained from 2 : 5-dichlorobenzoquinone and γ-mercaptobutyric acid, mixtures resulting, but the other quinone acids mentioned above were readily prepared by this method (see Experimental).

For comparison with the mercapto-acids the addition of thiophenol and propane-1-thiol (in equimolecular amounts) to benzoquinone was examined. Reaction was rapid at room temperature in aqueous suspension, thiophenol giving a mixture of 2 : 5- (13·5%) and 2 : 6-diphenylthiobenzoquinone (1%) and 2-phenylthiobenzoquinone (19%). Neither the tri- nor the tetra-substituted quinone was detected. Under different conditions (3 moles of quinone to two of thiophenol, in hot acetic acid) Dimroth, Kraft, and Aichinger (*Annalen*, 1940, **545**, 124) obtained mono-, di-, and tri-phenylthiobenzoquinones. Propane-1-thiol

afforded only 2 : 5-dipropylthiobenzoquinone (III; R = R′ = SPr^n). This was also obtained by reaction of 2 : 5-dichloroquinone with the potassium derivative of the thiol but we failed to obtain tetrapropylthiobenzoquinone by this method (cf. Tjepkema, *Rec. Trav. chim.*, 1952, **71**, 853).

Cunneen (*J.*, 1947, **36**, 134) has shown that the ease of addition of thiols to olefins is roughly parallel to their acidities; in particular he found thioglycollic acid to be more reactive than thiophenol. Our results confirm this general trend. The SH acidity of the mercapto-acids should diminish with increasing separation of the polar groups, and electrostatic interaction is probably negligible in γ-mercaptobutyric acid. In the reactions with benzoquinone γ-mercaptobutyric acid is less reactive than β-mercaptopropionic and thioglycollic acids and is comparable to propane-1-thiol. Thiophenol is slightly more reactive than γ-mercaptobutyric acid. These reactions are also affected by the nature of the solvent. This was observed by Dimroth *et al.* (*loc. cit.*) in the addition of thiophenol to benzoquinone, and in the case of thioglycollic acid reaction in chloroform gives two isomeric di-addition products (Gebauer-Fuelnegg and Jarsch, *J. Amer. Chem. Soc.*, 1930, **52**, 2451), whereas Snell and Weissberger (*ibid.*, 1939, **61**, 450) could only isolate a mono-addition product from the reaction in 95% alcohol.

Experimental

2 : 3 : 5 : 6-*Tetra(carboxymethylthio)quinol.*—To finely powdered 2-chlorobenzoquinone (1 g.) suspended in water (60 c.c.), thioglycollic acid (0·483 c.c.) was added during 5 minutes with stirring. Stirring was continued till dissolution was complete and the solution was then ether extracted (twice), and the extract dried ($MgSO_4$) and evaporated, yielding a dark oily residue. Repeated crystallisation from water gave needles, m. p. 276° (decomp.) (Found: C, 35·9; H, 3·2; S, 27·3. Calc. for $C_{14}H_{14}O_{10}S_4$: C, 35·8; H, 3·0; S, 27·2%). Schubert (*loc. cit.*) reported m. p. 288° (decomp.).

3 : 6- *and* 5 : 6-*Di(carboxymethylthio)toluquinol Dilactones* (VI).—A suspension of finely powdered toluquinone (10 g.) in water (200 c.c.) was treated with thioglycollic acid (5·7 c.c.), and stirred till a red solution was obtained. The solution became colourless overnight, and was then extracted twice with ether. The extracts were dried ($MgSO_4$) and evaporated. The residual yellow oil was heated at 190°/1 mm. to remove toluquinol (21% recovered). Fractional crystallisation of the solid residue from acetone yielded two *dilactones*, (*a*) m. p. 205—206° (placed in bath at 200°), and (*b*) less soluble, m. p. 235—236°, in approximately equal amounts (total yield 24%) [Found: (*a*) C, 48·8; H, 3·4; S, 23·7; (*b*) C, 48·8; H, 3·0; S, 23·6. $C_{11}H_8O_4S_2$ requires C, 49·3; H, 3·0; S, 23·9%].

Desulphurisation. The dilactone (0·3 g.) was refluxed in dioxan (15 c.c.) for 45 minutes with Raney nickel (3 g.). The mixture was filtered, the residue was extracted with boiling dioxan (2 × 10 c.c.), and the combined filtrates were evaporated to dryness. Vacuum-distillation of the oily residue gave a liquid which solidified overnight at 0° and had m. p. 43—44° [26% from (*a*), 39% from (*b*)]. A mixed m. p. with authentic toluquinol diacetate (m. p. 44°) was 43—44° (Schmid, *Monatsh.*, 1911, **32**, 437, reports m. p. 49°).

3 : 5 : 6-*Tri(carboxymethylthio)toluquinol Monolactone.*—A mixture of 3 : 5 : 6-trichlorotoluquinone (1·57 g.), water (100 c.c.), pyridine (0·5 c.c.), and thioglycollic acid (2·94 c.c.) was refluxed till a colourless solution was obtained. The solution was cooled, made alkaline with solid sodium carbonate, and extracted twice with ether. The solution was then acidified with concentrated hydrochloric acid (100 c.c.), and extracted with ether (twice). The extract was dried ($MgSO_4$) and evaporated, yielding a colourless oily residue, which solidified during 24 hours in a vacuum-desiccator. Recrystallisation from ethyl acetate–light petroleum (b. p. 100—120°) gave crystals, m. p. 164° (29%) (Found: C, 41·4; H, 3·4; S, 25·5. $C_{13}H_{12}O_7S_3$ requires C, 41·5; H, 3·2; S, 25·5%).

3 : 6-*Di(carboxymethylthio)*-2 : 5-*dimethylquinol.*—Thioglycollic acid (0·345 c.c.) was added to a suspension of *p*-xyloquinone (0·68 g.) in water (10 c.c.) at 60—70°, and this temperature was maintained with continuous stirring till dissolution was complete. The orange solution, on cooling, deposited a little dark oil (separated by decantation) and a white solid. After 1 hour at 0°, the latter was filtered off and washed with a little cold water. Recrystallisation from water yielded the *quinol* as crystals, softening 150—155°, m. p. 290—294 (decomp.) (50%). If placed in a bath at 160°, the acid melted immediately (Found: C, 45·3; H, 4·4; S, 20·1. $C_{12}H_{14}O_6S_2$ requires C, 45·2; H, 4·4; S, 20·1%).

3 : 6-*Di*(*carboxymethylthio*)-2 : 5-*dimethylbenzoquinone*.—The above quinol (0·15 g.) was dissolved in hot water (30 c.c.), and the solution was cooled to 35° and treated with a solution of potassium dichromate (0·5 g.) in water (1·5 c.c.) and concentrated sulphuric acid (0·5 c.c.). The mixture was cooled immediately in a freezing mixture; after 1 hour the orange precipitate was collected, washed with cold water, and recrystallised from water. The *quinone* separated as orange-red needles, m. p. 183° (75%) (Found: C, 45·4; H, 3·9; S, 20·0. $C_{12}H_{12}O_6S_2$ requires C, 45·6; H, 3·8; S, 20·25%).

m-*Xyloquinone*.—This was prepared (yield, 16%) from 2 : 6-dimethylphenol by the method of Smith, Opie, Wawzonek, and Prichard (*J. Org. Chem.*, 1939, **4**, 318) who used 3 : 5-dimethylphenol.

3 : 5-*Di*(*carboxymethylthio*)-2 : 6-*dimethylquinol*.—Thioglycollic acid (0·173 c.c.) was added to a suspension of finely powdered *m*-xyloquinone (0·34 g.) in water (5 c.c.). The mixture was stirred for 30 minutes, a small quantity of black material filtered off, and the red filtrate acidified with concentrated hydrochloric acid (1 c.c.) and kept overnight at 0°. The precipitate of *quinol* which formed was crystallised from 2N-hydrochloric acid, then having m. p. 154° (38%) (Found: C, 45·2; H, 4·6; S, 20·3. $C_{12}H_{14}O_6S_2$ requires C, 45·2; H, 4·4; S, 20·1%).

3 : 5-*Di*(*carboxymethylthio*)-2 : 6-*dimethylbenzoquinone*.—To the quinol (0·15 g.) dissolved in water (12 c.c.) at 20—25° was added with stirring a solution of potassium dichromate (0·5 g.) in water (1·5 c.c.), containing concentrated sulphuric acid (0·5 c.c.). The red precipitate which formed was filtered off after being kept at 0° overnight. Recrystallisation from water yielded the *quinone* as red needles, m. p. 174° (66%) (Found: C, 45·9; H, 3·8; S, 19·8. $C_{12}H_{12}O_6S_2$ requires C, 45·6; H, 3·8; S, 20·25%).

2-*Carboxymethylthio*-1 : 4-*naphthaquinone*.—To a stirred suspension of finely powdered 1 : 4-naphthaquinone (0·79 g.) in water (20 c.c.) at 40—50° thioglycollic acid (0·35 c.c.) was added, and the mixture was stirred at 40—50° for 15 minutes, heated to 70°, and decanted from a black tar. The precipitate (0·21 g.) which formed on cooling was collected after 3 hours, dissolved in water (50 c.c.), and oxidised by the addition of potassium dichromate (2 g.) in water (6 c.c.) containing concentrated sulphuric acid (2 c.c.). The *quinone* appeared immediately and was collected after chilling for 1 hour. Repeated crystallisation from water yielded yellow crystals, m. p. 172° (Found: C, 57·9; H, 3·5; S, 12·9. $C_{12}H_8O_4S$ requires C, 58·1; H, 3·2; S, 12·9%).

2-*Anilino*-1 : 4-*naphthaquinone*.—A mixture of 2-carboxymethylthio-1 : 4-naphthaquinone (0·12 g.), alcohol (5 c.c.), and aniline (0·05 c.c.) was refluxed for 1 hour. After being kept overnight at 0°, the product was filtered off and crystallised from aqueous alcohol, to give red needles, m. p. and mixed m. p. with 2-anilino-1 : 4-naphthaquinone 190—191° (42%).

2 : 3-*Di*(*carboxymethylthio*)-1 : 4-*naphthaquinol Dilactone* (V).—(*a*) The crude 1 : 4-naphthaquinone–thioglycollic acid addition product (0·84 g.) obtained as above was dissolved in pyridine (4 c.c.), and acetic anhydride (2 c.c.) added. A precipitate formed almost immediately and was collected after 1 hour. Recrystallisation from benzene yielded the dilactone in needles, m. p. 271—275° (decomp.) (11%).

(*b*) A mixture of 2 : 3-dibromo-1 : 4-naphthaquinone (0·15 g.) in water (5 c.c.), pyridine (0·05 c.c.), and thioglycollic acid (0·14 c.c.) was refluxed for 1 hour and the mixture filtered hot. The filtrate was chilled overnight, and the crude quinol which was deposited was washed with ice-cold water, dried, and dissolved in pyridine (0·5 c.c.). On addition of acetic anhydride (0·25 c.c.) crystals of the *dilactone* separated almost immediately. Recrystallisation from benzene afforded needles, m. p. 271—275° (decomp.) (47%), indistinguishable from those recorded in (*a*) (Found: C, 55·2; H, 2·6; S, 21·1. $C_{14}H_8O_4S_2$ requires C, 55·3; H, 2·6; S, 21·05%).

2 : 3 : 5 : 6-*Tetra*-(2-*carboxyethylthio*)*quinol*.—(*a*) β-Mercaptopropionic acid (0·434 c.c.) was added dropwise to a stirred suspension of finely powdered benzoquinone (0·54 g.) in water (15 c.c.). A bright red suspension was formed almost immediately. After 30 minutes' stirring the pale red suspension was filtered off, washed with water, and recrystallised first from glacial acetic acid and then from water (containing a trace of sodium dithionite), to yield the *quinol* in needles, m. p. 205—206° (12%). Addition of sodium hydrogen carbonate to the filtrate, and extraction with ether gave quinol, m. p. and mixed m. p. 172° (42%).

(*b*) A suspension of chloranil (0·246 g.) in a mixture of ethanol (15 c.c.), pyridine (1 c.c.), and β-mercaptopropionic acid (0·434 c.c.) was refluxed for 30 minutes and then evaporated to dryness. The residue crystallised from water in needles, m. p. 205—206° (53%) (Found: C, 41·2; H, 4·2; S, 24·4. $C_{18}H_{22}O_{10}S_4$ requires C, 41·1; H, 4·2; S, 24·3%).

2 : 3 : 5 : 6-*Tetra*-(2-*carboxyethylthio*)*benzoquinone*.—To 2 : 3 : 5 : 6-(tetra-2-carboxyethylthio)-quinol (0·15 g.) in water (30 c.c.) at 95° was added concentrated nitric acid (3 c.c.), and the

intense red solution immediately cooled to room temperature. After being kept overnight at 0°, the *quinone* was collected, washed with water, and crystallised from water in reddish-brown crystals, m. p. 194° (73%) (Found: C, 41·35; H, 4·0; S, 24·35. $C_{18}H_{20}O_{10}S_4$ requires C, 41·2; H, 3·8; S, 24·4%).

2-2′-*Carboxyethylthio*-1 : 4-*naphthaquinone*.—(*a*) Finely powdered **1 : 4**-naphthaquinone (0·79 g.) was stirred in water (30 c.c.) at 50—55° and β-mercaptopropionic acid (0·434 c.c.) added dropwise. Stirring was continued for 30 minutes at 50—55°. The mixture was then heated rapidly to 85°, and filtered from a black tar, the filtrate depositing a mixture of quinols (0·4 g.) on cooling, which was collected next morning and washed with water (see below). The black tarry residue was dried and stirred with a little ether, and the insoluble material crystallised from methanol in golden-yellow needles, m. p. 188° (13%). (*b*) A mixture of 2-bromo-1 : 4-naphthaquinone (0·35 g.), pyridine (0·5 c.c.), and β-mercaptopropionic acid (0·13 c.c.) in ethanol (8 c.c.) was refluxed for 30 minutes. The *quinone* separated on cooling, and crystallised from methanol in golden-yellow needles, m. p. 188° (43·5%), identical with those reported in (*a*) (Found: C, 59·2; H, 3·9; S, 12·3. $C_{13}H_{10}O_4S$ requires C, 59·5; H, 3·8; S, 12·2%).

2 : 3-*Di*-(2-*carboxyethylthio*)-1 : 4-*naphthaquinone*.—(*a*) The crude quinol mixture (0·4 g.) from the naphthaquinone–β-mercaptopropionic acid reaction (above) was dissolved in boiling water (30 c.c.). Concentrated nitric acid (5 c.c.) was added at 95°, a dark red solution resulting, which was immediately cooled in ice-water. The orange solid precipitated was crystallised from excess of ethanol, to give golden-yellow needles of 2-2′-carboxyethylthio-1 : 4-naphthaquinone (6·3%). The mother-liquor was evaporated to dryness and the residue recrystallised from ethanol. From the heterogeneous crystalline product obtained, the red crystals were mechanically separated and recrystallised from ethanol, to yield a small quantity of **2 : 3-*di*-(2-*carboxyethylthio*)-1 : 4-*naphthaquinone*** as brick-red crystals, m. p. 204°. (*b*) **2 : 3**-Dibromo-**1 : 4**-naphthaquinone (0·316 g.) was refluxed for 30 minutes in ethyl alcohol (5 c.c.) containing pyridine (0·5 c.c.) and β-mercaptopropionic acid (0·174 c.c.). A dark red solid formed on cooling, and crystallised from ethanol affording brick-red crystals, m. p. 204° (79%) (Found: C, 52·3; H, 3·9; S, 17·4. $C_{16}H_{14}O_6S_2$ requires C, 52·45; H, 3·8; S, 17·5%).

γ-Mercaptobutyric Acid.—This was prepared (52% yield) by the method of Holmberg and Schjånberg (*Arkiv Kemi, Mineral., Geol.*, 1940, **14**, *A*, No. 7) and had b. p. 102—103°/2·5 mm.

2 : 5(?)-*Di*-(3-*carboxypropylthio*)*benzoquinone*.—γ-Mercaptobutyric acid (1·545 c.c.) was added during 2 minutes to a stirred suspension of benzoquinone (1·62 g.) in water (60 c.c.). Stirring was continued for 30 minutes, and the product then filtered off, dried, and extracted with boiling chloroform (30 c.c.). The residue was crystallised from 50% aqueous alcohol, to yield red needles, m. p. 201—203° (12·4%) (Found: C, 48·6; H, 5·0; S, 18·6. $C_{14}H_{16}O_6S_2$ requires C, 48·8; H, 4·65; S, 18·6%). The filtrate was made alkaline with solid sodium carbonate and extracted with ether (twice), from which quinol, m. p. 172° (37%), was obtained.

2 : 3 : 5 : 6-*Tetra*-(3-*carboxypropylthio*)*benzoquinone*.—A mixture of chloranil (0·246 g.), pyridine (1 c.c.), and γ-mercaptobutyric acid (0·618 c.c.) in water (20 c.c.) was refluxed until an almost colourless solution was formed (*ca.* 15 minutes). Concentrated nitric acid (3 c.c.) was then added to the solution at 95°, and the whole immediately cooled to room temperature. The red precipitate formed was filtered off, and crystallised from aqueous acetic acid. The *quinone* formed reddish-brown crystals, m. p. 140° (50%) (Found: C, 45·8; H, 5·0; S, 22·3. $C_{22}H_{28}O_{10}S_4$ requires C, 45·5; H, 4·8; S, 22·1%).

Addition of Thiophenol to Benzoquinone.—To finely powdered benzoquinone (4·32 g.) suspended in water (140 c.c.), thiophenol (4·08 c.c.) was added during 5 minutes with stirring. A dark sticky solid was immediately formed. The suspension was stirred for 30 minutes, then extracted twice with ether. Evaporation of the extract to small bulk gave an orange solid. One crystallisation from glacial acetic acid yielded pure **2 : 5**-diphenylthiobenzoquinone in orange-red leaflets, m. p. and mixed m. p. with an authentic specimen (Dimroth, Kraft, and Aichinger, *loc. cit.*) 256—258° (8%). **2 : 6**-Diphenylthiobenzoquinone was isolated from the mother-liquor by dilution with water, and recrystallised from glacial acetic acid, to give brick-red crystals, m. p. and mixed m. p. 206° (1%).

The ethereal filtrate above was dried ($MgSO_4$) and evaporated, leaving a dark oily residue, which crystallised from benzene to give quinol, m. p. 172° (16%). Evaporation of the benzene mother-liquor to dryness again yielded a dark oil. Reductive acetylation of this with acetic anhydride (10 c.c.), zinc dust (1 g.), and pyridine (1 c.c.) gave, after fractional crystallisation from alcohol, two compounds: (*a*) less soluble, needles, m. p. 170° (5·5%), and (*b*) more soluble, needles, m. p. 84—85° (19%) (from aqueous alcohol). Mixed m. p. determinations showed

that (*a*) was 2 : 5-*diphenylthioquinol diacetate* and (*b*) 2-phenylthioquinol diacetate. (*a*) was also obtained by reductive acetylation of 2 : 5-diphenylthiobenzoquinone as above in needles, m. p. 170° (87%) (Found : C, 64·15; H, 4·4; S, 15·9. $C_{22}H_{18}O_4S_2$ requires C, 64·4; H, 4·4; S, 15·6%).

2 : 3 : 5 : 6-*Tetraphenylthiobenzoquinone*.—This was prepared from chloranil and potassium thiophenoxide according to Tjepkema (*loc. cit.*). It crystallised from glacial acetic acid in reddish-brown crystals, m. p. 176—177° (96%) (Found : C, 66·6; H, 3·75; S, 23·9. $C_{30}H_{20}O_2S_4$ requires C, 66·7; H, 3·7; S, 23·7%).

2 : 5-*Dipropylthiobenzoquinone*.—(*a*) Propane-1-thiol (0·91 c.c.) was added during 2 minutes to a stirred suspension of benzoquinone (1·08 g.) in water (35 c.c.), and stirring continued for 30 minutes. The dark red oily mixture obtained was extracted with ether, the extract evaporated to small bulk and the orange precipitate collected. Recrystallisation from ethanol yielded orange-red leaflets, m. p. 163° (10%). The ethereal filtrate was dried ($MgSO_4$) and evaporated, leaving a black residue which was crystallised from benzene giving almost pure quinol (40%).

(*b*) The potassium salt of propane-1-thiol (0·912 g.), dissolved in 50% aqueous alcohol, was added to 2 : 5-dichlorobenzoquinone (0·7 g.) suspended in ethyl alcohol (30 c.c.). The mixture was shaken for 3 hours, and the product precipitated from the dark red solution by dilution with water (50 c.c.). Crystallisation from ethanol afforded the *quinone* as orange-red leaflets, m. p. 163° (19%) (Found : C, 56·1; H, 6·2; S, 25·1. $C_{12}H_{16}O_2S_2$ requires C, 56·25; H, 6·25; S, 25·0%).

Analyses are by Miss M. A. Buchanan, and Drs. Weiler and Strauss, Oxford. We thank Dr. H. F. Bondy, of Coalite and Chemical Products Ltd., for a gift of 2 : 6-dimethylphenol, and the Department of Scientific and Industrial Research for a Maintenance Allowance (to A. B.).

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229. *The Properties of Freshly Formed Surfaces. Part XVIII.* Dynamic Surface Potentials and the Adsorption Process: Molecular Orientation in Soluble Films of Decyl Alcohol.*

By C. C. Addison and D. Litherland.

The adsorption of long-chain alcohols at a fresh water surface results in a rapid change of surface potential as well as of surface tension. An apparatus is described for the study of continuous changes in potential at fresh surfaces. Experiments on decyl alcohol solutions are recorded in which the rates of adsorption are sufficiently slow to enable rates of change of tension and potential to be compared. When concentration equilibrium between the surface and bulk solution is established, the surface tension shows no further change, but surface potential values show further pronounced changes which are interpreted as reflecting the rate of orientation of the disoriented film produced immediately adsorption is complete. When the soluble film has reached orientation equilibrium, the adsorption of additional solute (by further additions to bulk solution) disorients the film, and the influence of surface excess on rate of disorientation is considered. Unlike surface tension, which is relatively insensitive to changes in orientation, the surface potential of a solution depends as much on the condition of the adsorbed film as on the surface excess.

Previous papers in this series have been concerned with changes in the surface tension of aqueous solutions which occur immediately after the formation of a fresh liquid surface. Throughout this work a close relation has been observed between surface tension and surface excess, the latter being by far the major factor determining the surface tension of a solution. For any given surface excess, surface tension is influenced to a relatively small extent by changes in the orientation of adsorbed molecules. Under conditions (*i.e.*, rapid

* Part XVII, *J.*, 1950, 3103.

expansion of the surface) in which there must be considerable deviations from the equilibrium orientation, surface tensions are not greatly modified; thus for chain lengths below C_8 (Part XIV, *J.*, 1949, 3406) the relation between γ and Γ for rapidly expanding surfaces is the same as that for stationary surfaces. The disorientation of longer chains is reflected in a slight modification of the surface tension (Part IX, *J.*, 1948, 943; Part XIV, *loc. cit.*) but even then only when surface expansion is rapid and disorientation considerable. It appeared possible, however, that the orientation of an adsorbed molecule with respect to the surface might influence the air–water contact potential to a greater extent than the surface tension; this potential arises from the polar character of the water molecule, and the orientation of the hydrocarbon chains (and thus of the polar groups) in adsorbed molecules is likely to be of importance in determining the extent to which this air–water potential is modified.

It was therefore necessary, in initial experiments, to select a solute giving aqueous solutions in which the accumulation of surface excess is sufficiently slow to be measurable by both surface tension and surface potential techniques. Decyl alcohol is suitable, since adsorption continues for some minutes after formation of a fresh surface, and wide ranges of both surface tension and surface potential are available. The exploratory experiments on such solutions now described illustrate the pronounced sensitivity of surface potentials to orientation changes in adsorbed films of this kind.

Experimental

The apparatus used is indicated in Fig. 1. The contact potentials were obtained from the potential difference between a standard calomel half-cell in contact with the solution, and a

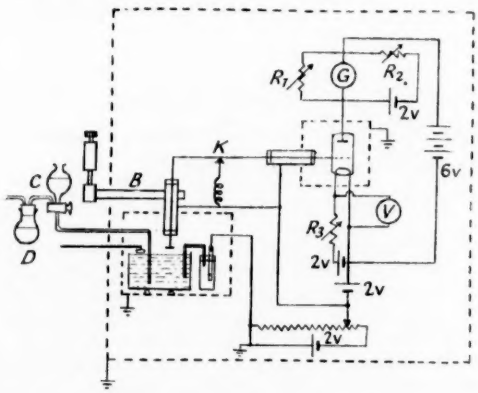


Fig. 1.
R_1 = 250 ohms.
R_2 = 10,000 ohms.
R_3 = 30 ohms.

radioactive electrode placed immediately above the surface. This potential difference was measured by an electrometer triode unit, incorporating a Wheatstone slide-back bridge circuit and galvanometer. The whole electrical circuit (including the batteries but excluding the galvanometer) was enclosed in an earthed cage of perforated zinc sheet, with detachable front, providing adequate screening from external electrical interference.

Valve.—A G.E.C. Type E.T.1 valve (filament voltage 1 v) was employed, enclosed in an earthed, airtight metal box. The valve holder was supported on an antimicrophonic mounting of sponge rubber. The base pins were connected directly to terminals on a Polythene panel on the side of the box. The control grid lead was taken from the box through a guard ring consisting of a 2-cm. brass tube fitted with polystyrene end plugs. (This lead, which was made as short as possible, passed directly and without further support to the air electrode terminal.) Before being fitted into the box, the glass surface of the valve was thoroughly cleaned with sodium-dried ether, and dried in a current of warm air. Before the box was sealed a dish of phosphoric oxide was put into it.

Air Electrode.—Radon needles mounted on copper electrodes were tried in preliminary experiments; ionisation of the air space was inadequate, and the galvanometer readings showed a continual drift. However, satisfactory electrical balance in the apparatus was obtained when

sufficient polonium was deposited on the electrode by direct displacement. When this deposition technique was used, copper was found to be unsuitable as an electrode metal, since its electrode potential ($-0{\cdot}34$ v) is below that of polonium ($-0{\cdot}4$ v). Zinc ($+0{\cdot}76$ v) is satisfactory, and the measurements described were carried out with zinc electrodes. A zinc cube (0·5 cm. edge) was soldered to the end of a brass rod (0·15 cm. diam. and 4 cm. long). The upper face and sides of the zinc block and the lower half of the rod were coated with picein wax. The lower face of the block was cleaned by filing it, and then immersed in 50 ml. of dilute hydrochloric–nitric acid solution prepared two years previously, containing $0{\cdot}81 \times 10^{-3}$ g. of radium per litre. Electrodes, dipped for 2, 12, and 27 minutes in this solution and allowed to dry in warm air, were placed 3 cm. from the window of a G.E.C. Type G.M.2 counter, and gave 4000, 9000, and 24,000 counts per minute respectively. (A similar copper electrode dipped for 15 minutes gave less than 1000 counts/min.) It was found that electrodes giving about 8000 counts/min. and upwards produced satisfactory ionisation of the air gap. With such electrodes the contact potential did not vary significantly with variation in the air gap up to about 5 mm. This is in agreement with observations by Harding and Adam (*Proc. Roy. Soc.*, 1932, **138**, *A*, 411). Nevertheless, in the present experiment the air gap was kept within the range 1·5—2·5 mm.

Temperature.—When the aqueous solution under test in the trough was at room temperature (at or near 20°) condensation took place on the air electrode; this resulted in loss of sensitivity and a continuous upward drift in the galvanometer readings. This difficulty was negligible when the solution was cooled, at the beginning of the experiment, to about 5° below room temperature. During an experiment the solution did not warm to room temperature; the sensitivity was checked at intervals during each experiment.

Air Electrode Mounting.—The electrode was coupled to the end of a brass rod (0·3 cm. diam. and 15 cm. long) passing centrally through a guard ring (2 cm. diameter, 10 cm. long) fitted with polystyrene end plugs. The guard ring was attached rigidly to one end of an ebonite bar 15 cm. long (*B*, Fig. 1), the other end of which was clamped to a worm-driven vertical rack mounted on the cage framework. The pitch of the worm drive was 1 mm., permitting accurate adjustment of the electrode position.

Standard Apparatus.—The potentiometer used was a Tinsley model, Type 3387 B, standardised by Weston cell. Since the instrument was used to give continuous readings, its galvanometer terminals were short-circuited and the key was permanently depressed. *G* (Fig. 1) was a Cambridge m/c spot galvanometer, with 16-cm. (centre zero) scale; to eliminate electrical interference, the lamp was run from a 6-v battery rather than a step-down transformer.

All batteries were of large capacity. After recharging, the apparatus was run for several hours to establish steady conditions. No switches were used, and terminals were soldered to short, stout, copper leads.

Manipulation.—To standardise the apparatus, the valve-filament heater was first connected, and resistance R_3 adjusted to give a potential drop of 1 v across the filament. With contact *K* closed and resistance R_1 short-circuited, all batteries were connected, bringing the valve grid to -2 v potential. The galvanometer sensitivity was increased by increasing R_1, and R_2 was simultaneously adjusted to maintain zero deflection. When steady conditions were reached (about 1 hour), R_1 was again reduced to protect *G*, the contact *K* was broken, and the air electrode lowered into position; R_1 was then slowly increased to give the desired sensitivity, and the potentiometer adjusted to restore zero galvanometer deflection. The galvanometer readings became steady 2—3 minutes after the air electrode had been lowered. At this stage, solute was added to the water in the trough. The subsequent changes in contact potential may be followed by continuous adjustment of the potentiometer to maintain zero deflection in *G* or by following the changes on the galvanometer scale, previously calibrated. The second (deflection) method was more convenient, and although the guard rings and valve grid may differ slightly in potential the insulating properties of polystyrene are sufficient to prevent leakage. The sensitivity was adjusted so that the 16-cm. galvanometer scale covered a range of ± 50 mv, and the potentiometer was adjusted in 100-mv steps when it was necessary to follow larger changes in contact potential.

Trough Arrangement.—A rectangular glass trough, 10·5 cm. deep, with ground and waxed rim was used. When it was filled to the rim, the liquid surface area was $10 \times 6{\cdot}2$ cm.^{2}, and the volume of liquid 650 ml. Before each experiment the trough was cleaned with hot alcohol–nitric acid mixture, and washed with clean tap-water: this gave the same results as distilled water, with less risk of grease contamination of the surface. At the beginning of each experiment the trough, calomel half-cell, and burette device for adding solute (*C*, Fig. 1) were placed in position, and a clean water surface obtained by running a stream of tap-water into the trough

for several minutes, with continuous overflowing. In experiments involving direct addition of decyl alcohol to the liquid surface, burette device *C* was not required; a waxed barrier was then fitted to the top of the trough to isolate the half-cell agar bridge, and the surface was swept by a movable barrier operated from outside the screening cage. To exclude draught, the trough was enclosed in an earthed metal box with transparent front.

FIG. 2.

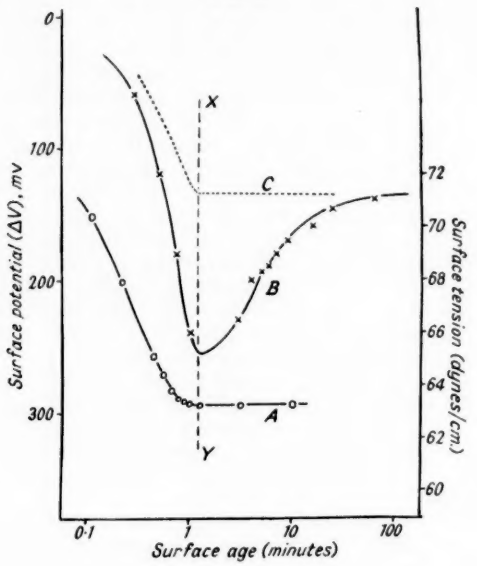
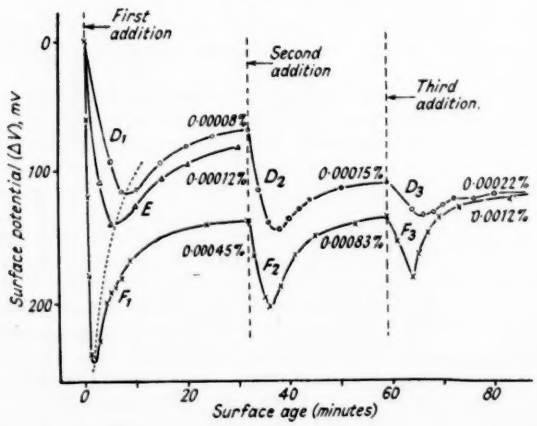


FIG. 3.



Addition of Solute.—When the electrical circuit was steady, 50 ml. of water were drawn from the trough by suction through the two-way tap into vessel *D*, and the solution in *C* (50 ml.) was immediately run into the trough. The latter operation required only a few seconds, but too rapid addition sometimes produced bubbles on the trough surface. Surface ages (Figs. 2 and 3) were timed from the instant when addition of solute was complete. The delivery tube extended to within 2 cm. of the bottom of the tank, and the circulation set up by the jet of liquid flowing from *C* rapidly established uniform concentration in the trough. This form of addition was specifically designed to avoid pouring through the surface, which leads (Part XII, *J.*, 1949, 3395) to the formation of a surface excess greater than that representing concentration equilibrium.

In successive addition experiments (Fig. 3) 50 ml. of decyl alcohol solution were removed from the trough and replaced by 50 ml. of a solution of higher concentration.

Blank experiments were carried out in which 50 ml. of water were withdrawn and replaced. This operation produced only a minor fluctuation of a few mv in the galvanometer reading. Since the introduction of decyl alcohol solution into the trough can give rise to rapid changes in contact potential, the response of the galvanometer readings to potential change was tested frequently.

Surface Tension.—The values recorded in Fig. 5 were determined by the vertical-plate method (Parts VII and XI, *J.*, 1948, 930; 1949, 3387).

Discussion

Curve *A* (Fig. 2) shows the change in surface tension of a 0·00045% solution of decyl alcohol at 15°. Immediately upon formation of a fresh surface, the tension falls, reaching a minimum of 63·3 dynes/cm. after 1 min. Thereafter, no further change occurs in the quantity of decyl alcohol adsorbed at the surface. Curve *B* shows the variations in the corresponding air–solution contact potentials. The potential at first falls rapidly from the air–water value through a range of 250 mv, reaching a minimum at the same surface age (1 min.) as that at which the surface tension becomes constant. However, the contact potential shows a considerable increase at surface ages beyond 1 min.; a steady value is reached within an hour, though the change in potential is almost complete within 30 min. In these papers the term surface potential is applied to the difference (ΔV) in potential between the air–water contact potential and that of the aqueous solution. The potential values are plotted in terms of ΔV, although in discussion of the experimental results it is usually more convenient to refer directly to the air–solution contact potentials.

Comparison of curves *A* and *B* at surface ages above the vertical line *XY* shows clearly that the potential values are influenced to a pronounced degree by some factor other than change in the quantity of alcohol adsorbed at the surface. These measurements may be readily interpreted on the basis that this additional factor is the change in orientation of the adsorbed molecules. During the adsorption process, molecules adsorbed at the surface will be prevented from achieving a state of stable orientation by the continual accumulation of adsorbate at the surface, and when adsorption is complete the film will therefore be in a disordered state. The subsequent rearrangement to a stable orientation involves no change in surface excess (Γ) and thus no change in surface tension, but is reflected in the pronounced rise in contact potential which commences immediately the adsorption process is complete. In earlier papers the term " equilibrium surface " (as opposed to " dynamic surface ") has been employed to signify a surface in concentration equilibrium with bulk solution. It is now necessary to qualify this term. Immediately the accumulation of adsorbate is complete, the surface is in a state of " disorientation equilibrium," and the results in Fig. 2 show that considerable intervals of time may elapse before this state changes to one of " orientation equilibrium."

The initial rapid fall in contact potential (curve *B*) therefore reflects the sum of two factors, *viz.*, surface excess and surface disorientation. If no disorientation occurred, the potential curve would have the form shown by the broken curve *C*. In view of the above, the potential representing orientation equilibrium is a characteristic physical property of the solution. Again, since molecular disorientation is at its maximum immediately the adsorption process is completed, the potential of the surface in this state is also a fundamental property of the solution.

The first section of Fig. 3 includes two additional potential–surface age curves obtained for lower decyl alcohol concentrations. The form of the curves is closely similar to curve *F* (*i.e.*, curve *B*, Fig. 2) so the general nature of the changes in potential occurring at a fresh surface is independent of concentration. The minima in the curves (connected by a broken line) occur at greater surface ages as concentration is decreased, and in each case the minimum occurs at the same surface age as that at which the corresponding surface tension becomes constant. At each concentration, orientation equilibrium is virtually complete within 30 min.; the relative position of the curves indicates that the surface potential both of the disorientated film (ΔV_d) and of the oriented film (ΔV_0) increase with increasing concentration.

Stepwise Increase in Concentration.—The second and the third section of curves *D* and *F* (Fig. 3) show the changes in potential which occur when additional solute is added to solutions which already carry adsorbed films in a condition of orientation equilibrium. The concentrations given on the curves represent the values to which the bulk concentration was increased at 32 and 59 min., respectively. In each case the contact potential shows an initial fall to a minimum, followed by a rise to the steady potential characteristic of orientation surface equilibrium at the new concentration.

FIG. 4.

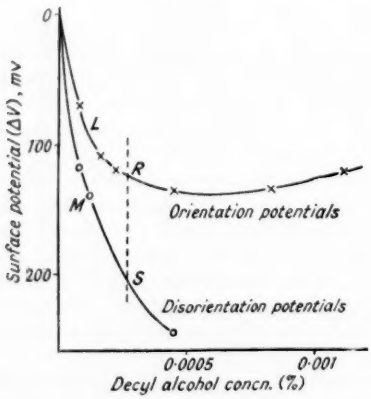


FIG. 5.

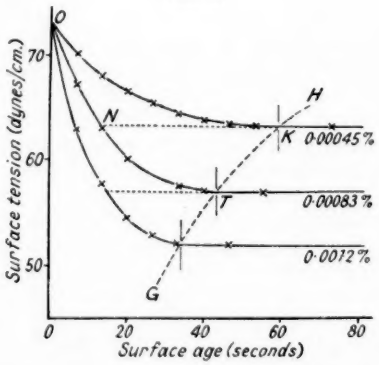


Fig. 4, curve *L*, shows the relation between V_0 and bulk concentration. Over a wide range of concentration the potential of the oriented film is almost independent of concentration, and only at the lowest concentrations does V_0 decrease with increasing concentration. The minimum cross-sectional area of long-chain primary alcohols, extrapolated to zero compression, is 21·6 Å^2 (Adam, "Physics and Chemistry of Surfaces," 3rd edn., 1941, p. 50). If each molecule is regarded as a cylinder, its diameter is therefore 5·24 Å. A length of 13·5 Å being assumed for the decyl alcohol molecule, the minimum permissible area occupied by each molecule lying flat in the surface is 70·7 Å^2, which is equivalent to a surface excess $\Gamma = 3{\cdot}72 \times 10^{-8}$ g./cm.^{2}. This Γ value corresponds to a bulk concentration of 0·00032% (Part XI, *loc. cit.*), and it is significant that the levelling of the V_0–concentration curve *L* commences at about this concentration. These results suggest that below this concentration the equilibrium orientation lies between two widely divergent limits, *i.e.*, the horizontal and the vertical positions, and variation in concentration can therefore influence to a considerable degree the mean position, and thus the potential. Above this concentration it is no longer possible for the molecules to achieve the horizontal position; the limits are therefore narrower, and change in concentration then has a small influence on the potential of the oriented film.

Extent of Disorientation.—Curve *M*, Fig. 4, was determined from measurements on the first addition of solute to water. The differences in potential between curves *L* and *M* therefore represent, at any concentration, the maximum possible influence of molecular disorientation. The addition to water of enough solute to bring the concentration immediately to the value represented by *RS* will cause the potential to decrease initially to *S*, and then to rise to *R*. If a solution of intermediate concentration is employed, which has been allowed to reach orientation equilibrium, and enough solute is then added to augment the concentration to *RS*, the adsorption process resulting from this second solute addition may be unable fully to disorient the film, and in consequence the minimum potential will not fall as far as *S*.

The results show that full disorientation can only occur when the adsorbed molecules are without mutual interference; any overlapping leads to lateral adhesion, which in turn restricts the disorientation of an oriented film. The maximum surface excess which can

be achieved without mutual interference between the adsorbed molecules is represented by a state in which the molecules lie in the plane of the surface, and occupy hexagonally close-packed circles whose diameter is equal to the length of the molecule. Calculation shows that for a decyl alcohol film in this state $\Gamma = 1{\cdot}67 \times 10^{-8}$ g./cm.^{2}, equivalent to a bulk concentration of 0·00015%. This is therefore the maximum concentration at which adsorbed molecules are independent of one another, and capable of maximum disorientation. This is illustrated by the results in Fig. 3. At the initial concentration of 0·00008%, the full disorientation effect is observed. On increase of concentration to 0·00015%, maximum disorientation is again observed, and the decrease in potential is equal to that which would be produced by the single-stage formation of a 0·00015% solution (Fig. 4). The third addition of solute gives a concentration (0·00022%) at which the adsorbed molecules must necessarily suffer some mutual interference. Opportunity for lateral adhesion then arises, and the possible disorientation of the adsorbed film by new adsorbing molecules is restricted. In consequence, the potential fall is small, and with each successive addition it continues to decrease. The same effect is apparent in the corresponding curves F_1, F_2, and F_3 obtained over a higher concentration range. Again, since high values of Γ necessarily limit the extent of possible disorientation, it is not possible to extrapolate curve *M* (Fig. 4) indefinitely. The particular conditions under which this curve may be extended to higher Γ values are discussed in the following paper.

Rates of Orientation and Disorientation.—The times required for the establishment of orientation equilibrium after the second and third addition of decyl alcohol are only a little less than the times (about 30 min.) within which orientation is substantially complete after the first addition. The small decrease in the orientation time may be related to the fact that (in curves D_3, F_2, and F_3, at least) the disorientation produced by addition of solute is not the maximum possible. In contrast, the rate at which an orientated film can be disorientated is much more rapid. Since in sections D_3, F_2, and F_3 (Fig. 3) the extent of disorientation is indefinite (lying somewhere between the curves *L* and *M*, Fig. 4), these falling sections of the curves are most appropriately interpreted by reference to the periods of time required to reach minimum potentials.

In experiments involving second and third additions of solute, it was first necessary to determine the time required for re-establishment of the equilibrium surface excess. The method employed is illustrated in Fig. 5, which shows full γ–surface age curves (15°) corresponding to the three concentrations employed in obtaining curves F_1, F_2, and F_3 (Fig. 3). The surface tensions are unchanged beyond the broken line *GH*. The surface excess present at the end of stage F_1 (Fig. 3) corresponds to the surface tension value of point *K* (Fig. 5), and the state of the surface immediately after the addition of a second quantity of solute is represented by point *N* (Fig. 5). As adsorption proceeds, the surface tension decreases along line *NT*, and the distance *NT* on the time axis gives the period necessary for re-establishment of the new surface excess. Similar conditions apply to subsequent additions. In the table below, the times required for disorientation of the adsorbed films are compared against the adsorption times for the concentrations involved in the curves *D* and *F* (Fig. 3).

Concn. increment (%)	Fig. 3 curve	Interval of time (seconds): (1) for adsorption of increment in Γ	(2) to reach minimum potential	Ratio (2)/(1)
0—0·00008	D_1	480	480	1
0·00008—0·00015	D_2	170	300	1·76
0·00015—0·00022	D_3	100	360	3·6
0—0·00045	F_1	60	60	1
0·00045—0·00083	F_2	48	240	5
0·00083—0·0012	F_3	20	300	15

Curves D_1 *and* F_1. The minimum potential is reached when adsorption is complete. Adsorbed molecules are disoriented as they arrive at the surface, and no disorientation time is therefore involved.

Curves D_2 *and* D_3. The adsorbed molecules in the oriented film at the beginning of D_2 have space for independent movement in any position. Nevertheless, the new molecules

being adsorbed at the surface are not able to disorient the film immediately, and the minimum potential is reached over a period which is almost twice that required for the adsorption process. Slight mutual interference (and lateral adhesion) occurs at D_3, and this is reflected in an increase in the disorientation/adsorption time ratio to 3·6

Curves F_2 *and* F_3. At these concentrations lateral adhesion in the equilibrium film is pronounced. The adsorption times in these cases represent a small proportion of the total time required for disorientation. The differing concentration levels in experiments *D* and *F* are reflected in the considerable difference in the rate at which the disorientation/adsorption time ratio increases on successive additions of decyl alcohol.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 30th*, 1952.]

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230. *The Properties of Freshly Formed Surfaces. Part XIX.* Dynamic Surface Potentials and the Desorption Process: the Spreading of Decyl Alcohol Films.*

By C. C. ADDISON and D. LITHERLAND.

When a film of decyl alcohol is spread on water, the adsorbed molecules are disoriented, and the subsequent variations in surface potential reflect the changes in molecular orientation as well as concentration in the adsorbed film. Similar measurements of potential changes during desorption into decyl alcohol solutions show that the extent of molecular disorientation produced in a spread film is determined by the rate of desorption from the film. Changes in potential produced on compression of an adsorbed film, and during subsequent desorption, are compared with those produced by spreading.

PART XII (*J.*, 1949, 3395) reported a study of the desorption of decyl alcohol from soluble films in which the surface excess was increased beyond the equilibrium value either by spreading the alcohol on the surface, or by pouring the aqueous solution of decyl alcohol from one vessel into another. The information available on the behaviour of the adsorbed molecules during the desorption process was limited by the relative insensitivity of surface tension to molecular orientation. Part XVIII * has shown that, for the adsorption process, further important properties of the film can be deduced from a parallel study of surface-potential changes. In view of this, the changes in surface potential occurring during desorption of decyl alcohol have been measured and are now described.

EXPERIMENTAL

The electrical apparatus employed was that described in the preceding paper, and the galvanometer-deflection method was used in measuring the contact potentials. The trough was modified for spreading experiments by removing the burette device used for addition of decyl alcohol solutions; the surface was swept by a waxed glass barrier which was drawn over the surface by means of an attached metal rod extending outside the screening cage. The film was applied by placing a measured quantity (up to 0·1 ml.) of a *n*-hexane solution of decyl alcohol on the surface from a microburette. The surface tension values recorded in Figs. 1, 4, and 5 were obtained by the vertical-plate method (Part VII, *J.*, 1948, 930).

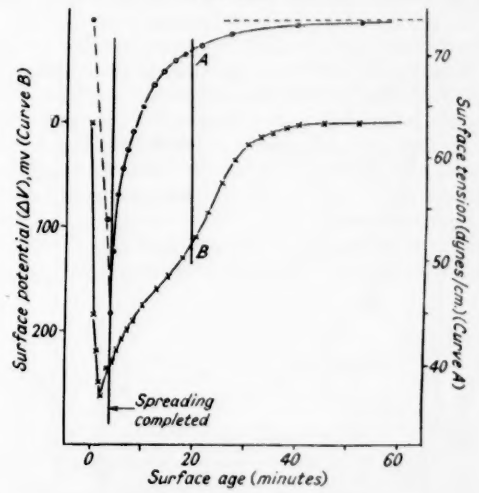
DISCUSSION AND RESULTS

Fig. 1 compares the changes in surface tension and surface potential which occur when 0·1 ml. of a solution containing 0·3 g./l. of decyl alcohol in *n*-hexane is added to a swept water surface at 15°. The surface area of the trough was 56 cm.^{2}, so the decyl alcohol added to the surface was equivalent to 4·4 times the quantity required to form a monolayer ($12{\cdot}2 \times 10^{-8}$ g./cm.^{2}). As the decyl alcohol spreads over the surface it is desorbed into the bulk solution, and the surface condition at any time is determined by the rates of spreading and desorption. When the quantity of alcohol added is eventually dispersed

* Part XVIII, preceding paper.

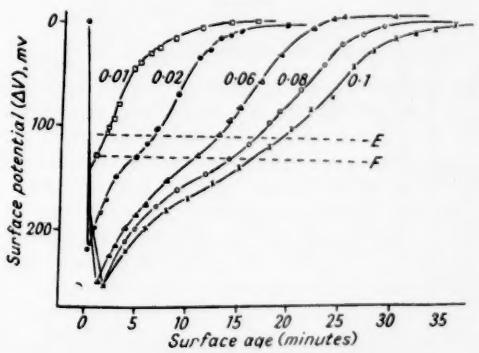
throughout the liquid, the bulk concentration is too small to give rise to any appreciable surface excess, so that after an initial rapid fall, both tension and potential return to the value for water. The differing positions of the two minima on the time axis are a character-

FIG. 1.



istic property of this system and have been observed in all experiments. The rise in surface tension follows a smooth curve but the potential curve shows a point of inflexion (*B*) at a surface age of about 20 min. At this stage the potential change is only half completed, whereas the surface tension (point *A*) has almost returned to the water value. It follows that beyond the vertical line *AB*, where the remaining surface excess is small, changes occur

FIG. 2.



in the film which influence the potential to a marked degree, but to which the surface tension is only slightly sensitive.

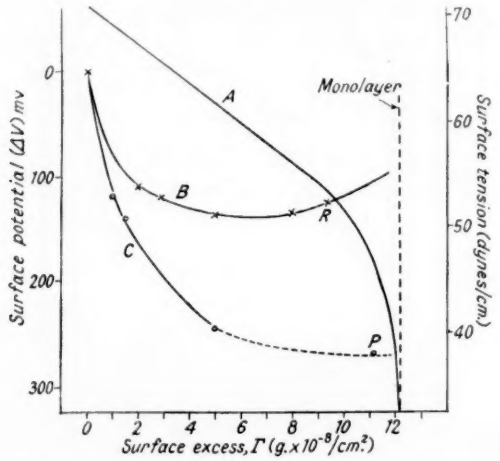
Fig. 2 shows the effect of spreading various quantities of decyl alcohol on water; the numbers on the curves refer to the volume (ml.) of decyl alcohol solution spread on the surface. For added quantities up to 0·02 ml. the minimum potential decreases, but thereafter the minimum is almost independent of the quantity of decyl alcohol spread. The times to reach minimum potential are given below:

Decyl alcohol solution added, ml.	0·01	0·02	0·04	0·06	0·08	0·10
Time to reach minimum (secs.)	<10	20	60	90	110	120

Each curve shows pronounced inflexion, and the position of the point of inflexion is a function of the potential (and thus the surface condition) rather than of the age of the surface.

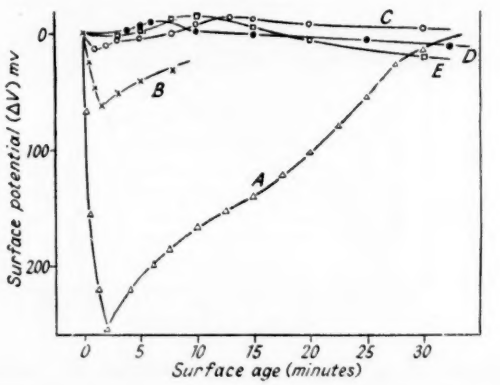
In order to interpret the potential changes, it is first necessary to consider the relative effect of surface excess on surface tension and potential (Fig. 3). The tension curve *A* is

FIG. 3.



derived from data given in Part XI (*J.*, 1949, 3387), and the orientation and disorientation potential curves (*B* and *C*, respectively) are derived from data in this and the preceding paper. At low Γ values the slope of curve *A* changes only slightly, but at high Γ values the curve approaches asymptotically the monolayer Γ value. Curve *B* illustrates the greater sensitivity of the orientation potential at low Γ values. The slope rapidly dimin-

FIG. 4.



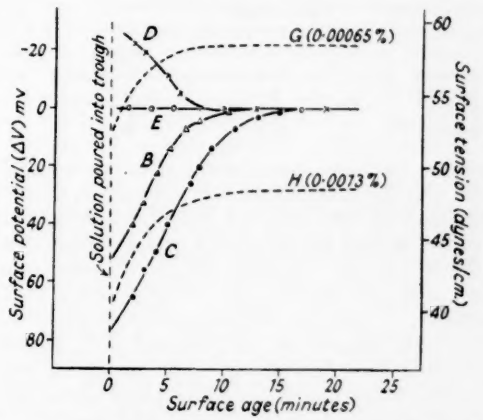
ishes, and over a wide Γ range the orientation potential is not greatly influenced by change in surface excess; as the monolayer is approached, curve *B* rises again. Beyond point *R*, the position of curve *B* is determined from the desorption curves for high concentrations given in Fig. 5.

At small Γ values, when the adsorbed molecules have ample space in which to depart from equilibrium orientation, experimental conditions under which the position of the disorientation-potential curve *C* can be determined are readily obtained. However, as the

molecules become more close-packed it is difficult to envisage conditions under which the film could undergo appreciable disorientation while still maintaining monolayer form, and at the limit it is not feasible to consider a disoriented monolayer. For this reason the part of curve *C* covering higher Γ values is shown as a broken line. Point *P* (curve *C*) represents the lowest potential obtained by spreading on water (Figs. 1 and 2); *P* bears no relation to curve *B*, but clearly falls on the disorientation curve *C*. Since *P* therefore represents a surface excess near the monolayer quantity which is fully disoriented, it must be assumed that when a decyl alcohol film is spread on water, the disturbance to which the surface film is subjected at the point of minimum potential is sufficiently vigorous to destroy a normal monolayer, and that the diffuse film is therefore more than one monolayer thick. It has been shown in Part XII (*loc. cit.*) that desorption from a decyl alcohol film into water is extremely rapid, and this is considered to be responsible for the disorganisation of the film.

The changes in tension and potential shown in Figs. 1 and 2 may be interpreted satisfactorily on this basis. It is known from visual observation that the minimum in the surface-tension curve (Fig. 1) coincides with the disappearance of the added lens of decyl alcohol–hexane solution. During the first 4 min., hexane is evaporating from the surface

FIG. 5.



of the solution; this process, together with rapid desorption, will maintain complete disorientation of the surface film, and it is significant that the potential reaches its minimum value during the course of the spreading (*i.e.*, after 2 min.) rather than when the lens disappears. The minimum surface tension reached is equivalent to a surface excess near that of a monolayer. That the film at this stage is a diffuse one rather than a monolayer of vertically oriented molecules is indicated by the subsequent potential changes. After the disappearance of the lens, the surface excess diminishes, but the rate of increase in potential is much greater than would result from change in surface excess alone (curve *C*, Fig. 3). The major factor is considered to be the change from a diffuse layer towards an oriented film, *i.e.*, the potential moves from curve *C* towards curve *B* (Fig. 3). However, the presence of a point of inflexion in the potential curve indicates that the orientation process does not proceed regularly. Whatever the quantity of decyl alcohol added to the surface, the point of inflexion lies (Fig. 2) within the band defined by the two horizontal broken lines *E* and *F*. Line *E* represents a surface excess of $1{\cdot}67 \times 10^{-8}$ g./cm.^{2}, which is the upper limit at which the adsorbed molecules are free from mutual interference. Line *F* ($\Gamma = 3{\cdot}72 \times 10^{-8}$ g./cm.^{2}) represents the maximum surface excess at which the molecules can lie horizontally in the surface when packed as parallel cylinders; under these conditions it is still possible for maximum disorientation to occur but some mutual interference will no doubt arise. The change is slope of the potential curves (Fig. 2) may therefore be explained in two closely related ways. (*a*) Up to the band *EF* the surface excess is high, and is in the Γ range where variation in this excess has little influence on the poten-

tial values. The change in potential is then due almost entirely to the orientation factor. When Γ is reduced to the EF band region, both orientation and disorientation potentials are sensitive to surface excess (Fig. 3), so the surface concentration effect is added to the orientation effect, and the increase in potential becomes more rapid. (*b*) Below the band EF, the rate of orientation is reduced by the mutual interference of adsorbed molecules. As Γ passes through the band EF, the adsorbed molecules become free from mutual interference, with consequent increase in the orientation rate.

Spreading on Decyl Alcohol Solutions.—When a film is spread on water, the disorientation of the film arises predominantly from the high rate of desorption. It follows that if the rate of desorption can be reduced there should be less disorientation in the film, and a smaller change in potential. The rate of desorption can be suitably reduced by spreading the decyl alcohol film on an aqueous solution of the alcohol instead of on water. Evidence given in Part XII (*loc. cit.*) showed that the rate of desorption is determined by the difference $\Delta\Gamma$ between the actual surface excess and that representing equilibrium with the bulk solution. The following results give the desorption rates which are observed when a film approximating to a monolayer is spread on decyl alcohol solutions of different concentrations :

Curve (Figs. 4 & 5)	Decyl alcohol concn., %	Equilibrium Γ (g. $\times$ 10^{-8}/cm.^{2})	$\Delta\Gamma$	Desorption rate $-d\Gamma/dt$ (g. $\times$ 10^{-11}/cm.^{2}/sec.)
A	Nil	0	12·2	Very rapid
B	0·00016	1·9	10·3	84
C	0·00065	6·7	5·5	20
D	0·0013	9·9	2·3	7
E	0·0026	12·1	0·1	1

The desorption rates are decreased considerably with increasing concentration of decyl alcohol in bulk solution, and the influence of this decrease is shown in Fig. 4, where the dynamic potentials obtained on spreading 0·1 ml. of the decyl alcohol–hexane solution on aqueous solutions of the alcohol are compared with the results of spreading on water. Even with the most dilute solution employed (curve *B*), disorientation by desorption is considerably diminished, and at 0·00065% the initial decrease in potential on spreading the film has almost vanished. At higher concentrations no disorientation occurs, and the spreading of the film has little influence on the potential of the surface.

Disorientation of Adsorbed Film by Pouring.—The desorption studies in Part XII (*loc. cit.*) showed that the surface excess could also be increased above the equilibrium value by pouring the decyl alcohol solution from one vessel into another. To compare the two methods of producing a high Γ value (*i.e.*, spreading and pouring) solutions having the concentrations employed for curves *B*, *C*, *D*, and *E* (Fig. 4; above table) were each poured steadily into the trough, and the electrode was lowered rapidly into position; the changes in potential observed are shown in Fig. 5. The four curves are referred to a common equilibrium potential (although the actual contact potentials differed) since the surface potentials (ΔV) may then be compared directly with the values in Fig. 4. At the lower concentrations (curves *B* and *C*) the large increase in the potential values indicates some disorientation in the original film, but at higher concentrations (curves *D* and *E*) no rise occurs, and the pouring process is evidently unable to bring about disorientation. As with the spreading process, the nature of the potential changes is fundamentally altered by change in bulk concentration, although the general nature of the surface-tension curves *G* and *H* superimposed in Fig. 5 is not correspondingly influenced by concentration change.

It may be deduced from the surface-tension data that the pouring of solutions *B* and *C* (Fig. 5) produces initial Γ values of about 5·0 and 9·3 $\times$ 10^{-8} g./cm.^{2}, respectively. If these quantities were fully disoriented, Fig. 3 indicates that the subsequent increases in potential would be 130 and 160 mv, respectively. The observed potential changes are 55 and 80 mv, so the compression of the surface film by pouring is inadequate to bring about complete disorientation. The compression produced by pouring solution *D* raises Γ from the equilibrium value of 9·9 to 11·9 $\times$ 10^{-8} g./cm.^{2}. With surface excess of this order it is not possible by this technique to produce disorientation in the film, and the small decrease in potential which is shown in curve *D* (Fig. 5) is entirely a surface concentration factor,

and corresponds with the slope of the orientation potential curve *B* (Fig. 3) in this Γ range. The equilibrium Γ for solution *E* is $12{\cdot}1 \times 10^{-8}$ g./cm.^{2}. Compression by pouring, and subsequent desorption, is therefore small in the case of this near-monolayer, and in consequence no change in potential is detectable.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 30th*, 1952.]

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231. *The Properties of Freshly Formed Surfaces. Part XX.* An Examination of the Use of Dynamic Surface Potentials in the Study of Adsorption Rates.*

By C. C. ADDISON and D. LITHERLAND.

The discrepancy between the dynamic surface tensions of aqueous solutions of *iso*amyl and *sec.*-octyl alcohols, measured by Addison (Parts II and III, *J.*, 1944, 252, 477) from the dimensions of an oscillating jet of solution, and those deduced by Posner and Alexander (*Trans. Faraday Soc.*, 1949, **45**, 651) from measurements of surface potentials along the liquid jets has been investigated. Measurements of the change in surface potential with time for solutions of these alcohols show that the disorientation potentials operative during and immediately after completion of the adsorption process differ considerably from the equilibrium orientation potentials of these solutions. When Posner and Alexander's potential measurements are translated into dynamic surface tensions by use of the disorientation potential–tension relation characteristic of the jet surface, the dynamic tensions determined by the two methods are in close agreement.

A KNOWLEDGE of the change of surface tension during the accumulation of an adsorbed film at a fresh surface is almost indispensable in studies of adsorption mechanism. Except for extremely dilute solutions, the adsorption process in aqueous solution is normally completed within one second, and special experimental techniques are necessary for measurement of the rapid tension changes involved. The only comprehensive study of these dynamic surface tensions at present available is that described by Addison (Parts I—V, *J.*, 1943, 535, *et seq.*) in which the dynamic surface tensions of aqueous solutions of long-chain alcohols were derived from measurements of the changing wave-lengths along an oscillating jet of solution; various workers, *e.g.*, Blair (*J. Chem. Phys.*, 1948, **16**, 113) and Ward and Tordai (*ibid.*, 1946, **14**, 453), have relied upon the validity of these measurements in their considerations of the adsorption process. However, the dynamic tensions of aqueous solutions of *iso*amyl and *sec.*-octyl alcohols determined by Posner and Alexander (*loc. cit.*) differed appreciably from the values reported in early papers in this series. These authors determined the change in potential along a liquid jet, and translated these potentials into surface tensions by means of a calibration curve derived from static measurements of potential and tension at equilibrium surfaces.

This paper describes an examination of the relation between surface potentials and surface tensions at fresh surfaces of aqueous solutions of these two alcohols. Posner and Alexander's calculations (*loc. cit.*) are in error in that they take no account of the fact that the potential which is operative at the surface of a liquid jet to which solute is adsorbing is a disorientation potential (Part XVIII, *J.*, 1953, 1143), which differs from the value measured at an equilibrium surface by an amount (often considerable) which varies with chain length and concentration of solute. When Posner and Alexander's potential measurements are correctly interpreted, the dynamic tensions derived therefrom are in almost complete agreement with the values calculated directly from jet dimensions (Parts II and III, *loc. cit.*).

RESULTS AND DISCUSSION

iso*Amyl Alcohol.*—Curves *A*, *B*, and *C* (Fig. 1) refer to aqueous solutions of *iso*amyl alcohol. The technique employed has been described in detail in Part XVIII (*loc. cit.*). The curves in Fig. 1 trace the changes in potential which occurred immediately after the addition of the alcohol solution. Equilibrium was established within 10 minutes, and for

* Part XIX, preceding paper.

each concentration a series of further additions was then made. The concentrations in the trough represented by each section of each curve are given in the following Table:

Curve (Fig. 1)	Concn. (%) of added 25 ml. of *iso*amyl alcohol solution	Trough concn. (%) following: 1st addtn.	2nd addtn.	3rd addtn.	4th addtn.
A	0·35	0·0135	0·026	0·039	—
B	0·82	0·032	0·0635	0·0925	—
C	1·84	0·071	0·139	0·203	0·266

The initial rapid adsorption of *iso*amyl alcohol gives a disoriented film, and equilibrium orientation is only reached after several minutes. There is a difference of up to 100 mv in

FIG. 1.

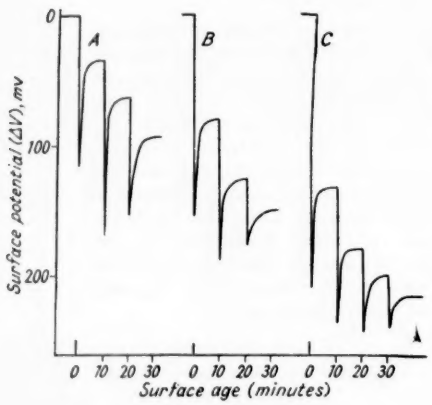
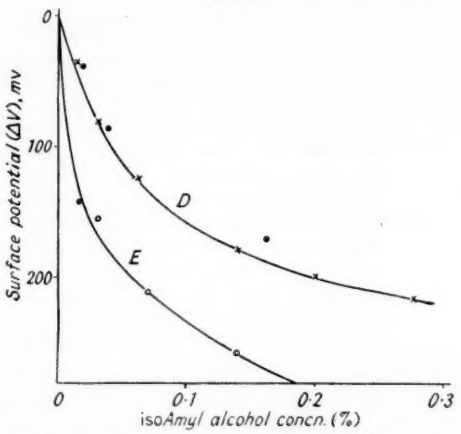


FIG. 2.



× × Orientation potentials (this work).
● ● Surface potentials (Posner and Alexander).
○ ○ Disorientation potentials (this work).

FIG. 3.

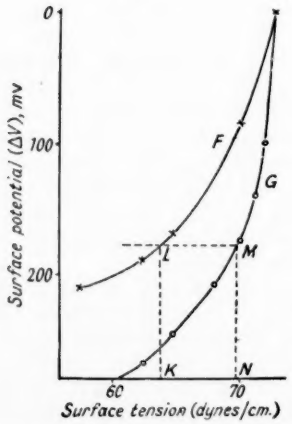
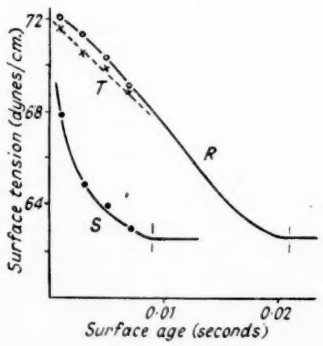


FIG. 4.



the potential of the surface in its two limiting states. On first addition of alcohol to the trough the minimum potential is reached within 20—30 seconds; the adsorption process is complete within 1 second, but since the apparatus is not able to respond immediately to potential changes of this rapidity, the initial measured rates of potential change are slower than those actually occurring. However, the subsequent rate of increase in potential is so much slower than the initial rate of decrease that the minimum potentials recorded on first addition of alcohol may be accepted as representing the potential of the fully disoriented film. At all stages during the adsorption process the adsorbed molecules are disoriented, and these experimental conditions hold at the surface of a liquid jet to

which solute is being adsorbed. Although the state of orientation has little influence on surface tension (and thus on the physical dimensions of an oscillating jet), the potential at the jet surface will differ considerably from that at a surface at which the same quantity of adsorbate has been allowed to reach orientation equilibrium.

From experiments of the type illustrated in Fig. 1, the orientation potential–concentration curve has been determined, and is shown in Fig. 2 (curve *D*). The equilibrium values determined by Posner and Alexander (*loc. cit.*) are superimposed in Fig. 2, and lie close to curve *D*. Curve *E* (Fig. 2) is the disorientation potential–concentration curve, determined from first additions of *iso*amyl alcohol to water. Except in the most dilute solutions (*e.g.*, second addition, curve *A*, Fig. 1) the adsorption of *iso*amyl alcohol is not able to bring about complete disorientation of a surface at which an oriented film already exists; as with decyl alcohol (Part XVIII, *loc. cit.*) the disorientation potentials obtained by successive addition of alcohol to the same solution lie between curves *D* and *E* (Fig. 2).

FIG. 5.

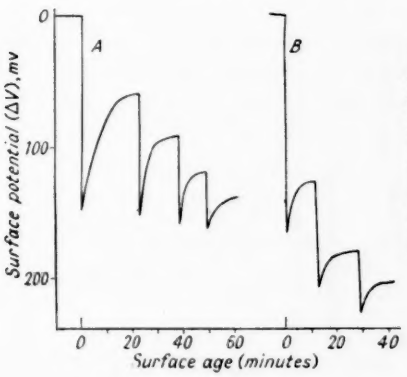
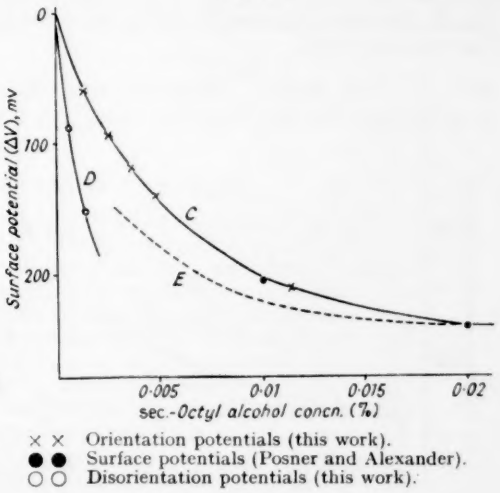


FIG. 6.



× × Orientation potentials (this work).
● ● Surface potentials (Posner and Alexander).
○ ○ Disorientation potentials (this work).

Curve *F* (Fig. 3) is the calibration curve relating the orientation potentials and surface tensions determined in these experiments. Posner and Alexander (*loc. cit.*) do not give all the relevant experimental data, but the calibration curve employed would lie close to curve *F* (Fig. 3). These authors were in error in employing this curve, and the operative dynamic tensions should be obtained by using the disorientation potential–tension curve *G*. The true dynamic tensions have therefore been obtained from Posner and Alexander's data as follows. The reported dynamic tension value (*K*, Fig. 3) is assumed to have been obtained from a measured potential represented by point *L*. Curve *G* being used instead of *F*, point *L* is transferred to *M*, giving a true dynamic tension shown by point *N*.

Curve *R* (Fig. 4) was determined (Part II, *loc. cit.*) from the change in wave-length along an oscillating jet of 0·162% *iso*amyl alcohol solution. Curve *S* shows the tensions reported by Posner and Alexander (there is a discrepancy of 2·6 dynes/cm. between the two equilibrium values for the surface tension of this solution, and Posner and Alexander's values have been advanced on the tension axis by this amount to facilitate direct comparison). Curves *R* and *S* give widely differing values for the time required to complete the adsorption process (0·021 and 0·009 second, respectively). However, when the points on curve *S* are translated in the manner described, curve *S* moves to the position shown by the broken curve *T* (Fig. 4), which is very close to curve *R*. It follows that in the *iso*amyl alcohol system, adsorption rates determined from both jet dimensions and surface potentials are in agreement provided that the variation in surface potential with surface condition is recognised.

sec.-*Octyl Alcohol.*—Surface potential–time curves for *sec.*-octyl alcohol are given in Fig. 5. The orientation process is slower than with *iso*amyl alcohol. The trough concentration after each addition is given in the following table :

Curve (Fig. 5)	Concn. (%) of added 25 ml. of *sec.*-octyl alcohol solution	Trough concn. (%) following : 1st addtn.	2nd addtn.	3rd addtn.	4th addtn.
A	0·0335	0·0013	0·0025	0·0037	0·00485
B	0·103	0·004	0·0077	0·0115	—

The disorientation produced by successive additions of *sec.*-octyl alcohol to the same solution is again less than the maximum possible. The orientation potential–concentration curve is shown as curve *C*, Fig. 6. Posner and Alexander's equilibrium values have been superimposed, and show exact agreement. It was not possible to extend the disorientation potential curve *D* beyond the low concentration range shown; when the surface excess becomes sufficiently great to involve lateral adhesion of adsorbed molecules, the adsorption process does not produce complete disorientation. In consequence, the rise from the first minimum in curve *B* (Fig. 5) is much less than in curve *A*. The disorientation curve *E* (Fig. 6) illustrates the comparatively small disorientation effect produced over the higher concentration range.

FIG. 7.

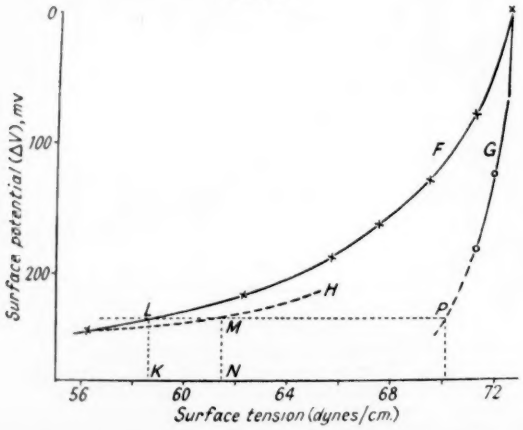
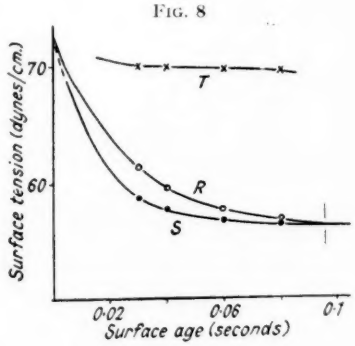


FIG. 8



The corresponding potential–surface tension calibration curves are shown in Fig. 7; the difference between dynamic tensions deduced by using orientation or disorientation potentials clearly depends upon the concentration of the solution under test. Posner and Alexander observed, in the case of *sec.*-octyl alcohol solutions, only small differences between tensions calculated from orientation potentials and those determined directly from jet dimensions; this arises from the fact that at the particular concentration employed (0·02%) the disorientation potential curve *H* (Fig. 7) lies close to the orientation potential curve *F*. The dynamic surface tension–time curve obtained from wave-length measurements (Part III, *loc. cit.*) is shown as curve *R* in Fig. 8. After adjustment on the tension axis to allow for a 2·9 dynes/cm. discrepancy in the equilibrium tension of the solution, the results deduced by Posner and Alexander from an orientation potential–tension calibration curve are shown as curve *S*, Fig. 8. The difference between the curves is small compared with the case of *iso*amyl alcohol, and each curve indicates that adsorption is complete at about 0·1 second. The experimental values on curve *S* (Fig. 8) may be translated as described for *iso*amyl alcohol solutions. The reported tension value *K* (Fig. 7) was derived from the measured potential *L*. If *L* is translated to point *M* on the disorientation curve *H*, then the small increase in tension from *K* to *N* is sufficient to raise curve *S* (Fig. 8) into a position in almost exact agreement with curve *R*. If the full disorientation curve *G* (Fig. 7) is extrapolated to the higher concentration range, translation of point *L* (Fig. 7) to point *P* involves a large increase in tension, and raises curve *S* (Fig. 8) to the position shown by

curve T. It is clear therefore that at the high concentration used the state of the surface is correctly represented by the calibration curve H (Fig. 7). It follows from these considerations that if Posner and Alexander had applied their technique to the dilute solutions where full surface disorientation was possible, a larger discrepancy would have been observed between their derived dynamic tensions and those measured directly from jet dimensions.

It is necessary, in conclusion, to compare the suitability of these two techniques for the determination of dynamic surface tension. Posner and Alexander state that the potential method " with its freedom from the theoretical difficulties associated with the oscillatory-jet technique, is more likely to give the correct results." When the state of the surface under test is known, and the appropriate potential–tension relation employed, the two methods yield the same results. The potential method, however, has the disadvantage that it is necessary in all cases to carry out a separate study, often of some complexity, into the nature of the surface involved, before it is possible to translate the measured potentials into dynamic tensions.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 30th*, 1952.]

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232. *The Properties of Freshly Formed Surfaces. Part XXI.* The Influence of Chain Length and Structure on the Surface Potentials of Aqueous Solutions of Alcohols.*

By C. C. ADDISON and D. LITHERLAND.

Orientation and disorientation surface potentials have been measured for aqueous solutions of ethyl, *n*-propyl, *n*-butyl, *n*-amyl, and *n*-hexyl alcohols. When the equilibrium (orientation) potentials ΔV_0 are plotted against surface excess Γ for the C_2—C_5 alcohols, the points lie on a common line. The constant value of the measured dipole moment ($\mu = 223$ mD) indicates that the tilt of the dipole to the surface is independent of chain length over this range. Hexyl and higher alcohols show some deviation; possible reasons for this are considered. The disorientation produced by adsorption ($\Delta V_d - \Delta V_0$) is studied as a function of chain length and surface excess. For any given surface excess, disorientation increases with chain length up to C_5, after which the effect diminishes. The results are interpreted on the basis of the temporary displacement of the dipole from the orientation position, and the disorientation of associated water molecules in the surface. The degree of disorientation produced by further adsorption to a surface carrying an equilibrium film has been studied. For dilute solutions of the shorter-chain alcohols (*e.g.*, *n*-propyl), the disorientation is no more than that equivalent to the increment in Γ. At the higher Γ values given by longer-chain alcohols the disorientation is diminished by mutual interference in the film. The curiously slow rate of orientation of a disoriented film is also discussed.

The influence of chain structure on surface potential is considered in the light of results for *iso*butyl, *iso*amyl, *tert.*-butyl, and *tert.*-amyl alcohols. *tert.*-Butyl alcohol ($\mu = 460$ mD) is unique in that its symmetrical structure renders its vertical orientation to the surface highly probable. On this assumption, the angle of tilt of the dipole to the vertical (θ) is calculated, the value to be attributed to the dielectric constant ε in the application of the Helmholtz equation $\Delta V = 4\pi n\mu$ is deduced, and this value of ε employed in the calculation of θ for the straight-chain alcohols.

Surface potential and tension measurements for ethylene glycol and for butane-1 : 3-diol are presented for comparison with the monohydric alcohols. Each compound gives the same value (*ca.* 850 mD) for the total dipole moment.

THE measurements now described were carried out to determine how far the general relations between surface potential and orientation already outlined are modified by

* Part XX, preceding paper.

variation in the length and structure of the carbon chain. Frumkin (*Z. physikal. Chem.*, **1924**, **111**, 195) and Pankhurst (*Proc. Roy. Soc.*, 1942, *A*, **179**, 393) have determined equilibrium surface potentials for a few alcohols, but the available evidence is insufficient for a comprehensive study. Both orientation and disorientation potentials have therefore been measured for aqueous solutions of the ethyl–hexyl series of straight-chain alcohols at 16°, and the results are collected in Table 1. In each case the concentration range employed is chosen so as to lie wholly, or mainly, below the concentration at which mutual interference of adsorbed molecules will arise, so that the effects observed may be related directly with the structure of the solute molecule concerned. The relevant concentrations are given below :

Alcohol	Ethyl	*n*-Propyl	*n*-Butyl	*n*-Amyl	*n*-Hexyl	*n*-Decyl
Concn., %	(mono-layer)	(mono-layer)	2·0	0·20	0·043	0·00015

These concentrations are calculated on the assumption that the adsorbed molecules lie flat in the surface, and form the diameters of hexagonally close-packed circles. With ethyl and propyl alcohol, the area of such a circle is near the cross-sectional area of the head-group, so that little mutual interference occurs at any concentration. At the highest concentrations used (1·45 and 1·20%, respectively) the Γ values are 1·0 and $2{\cdot}2 \times 10^{-8}$ g./cm.^{2}, compared with 3·5 and $4{\cdot}6 \times 10^{-8}$ g./cm.^{2} for the monolayers.

TABLE 1.

Ethyl alcohol				n-*Propyl alcohol*				n-*Butyl alcohol*			
C, %	ΔV_0	ΔV_0 †	ΔV_d	C, %	ΔV_0	ΔV_0 †	ΔV_d	C, %	ΔV_0	ΔV_0 ‡	ΔV_d
0·385	40	—	60	0·028	5	—	28	0·025	15	—	124
0·475	47	50	—	0·128	34	—	104	0·060	33	—	149
0·755	68	—	88	0·155	50	—	110	0·100	60	43	178
0·792	70	75·5	—	0·240	74	54	140	0·120	68	—	182
1·105	88	—	110	0·300	92	—	—	0·240	130	—	226
1·450	100	—	132	0·360	—	—	168	0·300	144	129	234
				0·470	131	—	170	0·358	154	—	250
				0·582	—	—	190	0·470	164	—	252
				0·680	152	—	—	0·500	171	165	260
				0·885	160	—	214	0·580	184	—	—
				0·975	176	—	—	0·690	180	—	—
				1·20	182	187·5	—	0·920	200	—	—
								1·000	204	209	—

n-*Amyl alcohol*				n-*Hexyl alcohol*			
C, %	ΔV_0	ΔV_0 *	ΔV_d	C, %	ΔV_0	ΔV_0 *	ΔV_d
0·01	20	—	112	0·0040	48	—	121
0·022	45	—	—	0·0080	62	—	145
0·030	—	—	203	0·0195	98	—	210
0·040	80	—	—	0·0250	124	—	—
0·050	96	85	230	0·0300	127	63	246
0·061	112	—	246	0·0375	140	—	—
0·089	144	—	256	0·0570	164	—	—
0·100	151	113	268	0·0740	175	—	—
0·118	160	—	—				
0·145	174	—	—				

* Pankhurst's results (*loc. cit.*) † Frumkin's results (*loc. cit.*).
‡ Adam, Askew, and Pankhurst's results (*Proc. Roy. Soc.*, 1939, *A*, **178**, 485).

Frumkin obtained the quoted values of ΔV_0 for ethyl and *n*-propyl alcohol by using the method of flowing junctions, and Table 1 shows that the results obtained by these two widely differing techniques are in reasonable agreement. Adam, Askew, and Pankhurst (*loc. cit.*) used a radioactive electrode technique similar to that employed in the present work. Except for the very dilute solutions, the ΔV_0 values for *n*-butyl alcohol are in good agreement, but the present values for *n*-amyl and for *n*-hexyl alcohol solutions are greater than the values given by Pankhurst (*loc. cit.*) for these solutions.

Equilibrium (Orientation) Surface Potentials.—When the equilibrium surface potential values are plotted against the logarithm of the molar concentration, a series of nearly parallel lines is obtained, indicating that Traube's rule is applicable to the surface potentials

of this homologous series. The mean molar concentration ratio for each increment in chain length (between C_2 and C_6) is given below for a range of ΔV_0 values :

ΔV_0	40	60	80	100
C_{n+1}/C_n	3·81	3·73	3·60	3·65

The concentration–potential curve for decyl alcohol reported in Part XVIII (*loc. cit.*) lies close to the position calculated from the above ratios. Frumkin (*loc. cit.*) obtained a mean value for C_{n+1}/C_n of 3·65 for the straight-chain fatty acids. The mean value of C_{n+1}/C_n determined from the surface tensions of these alcohols (Part IV, *J.*, 1945, 98) is 3·23.

The values of ΔV_0 given in Table 1, together with the decyl alcohol values, are plotted in Fig. 1 against the corresponding molecular surface excess; the latter values were determined by applying Gibbs's equation to the surface-tension data given in Part IV (*loc. cit.*). The points for all alcohols up to C_5 lie close to a straight line passing through the origin. Substitution of the slope of this line in Helmholtz's equation $\Delta V/n = 4\pi\mu$ (where $n = \Gamma$ when the latter is expressed as molecules/cm.^{2}) gives a value of 223 mD for the dipole moment μ, which agrees closely with the value of about 230 mD found from insoluble monolayers of the higher homologues (Adam, " The Physics and Chemistry of Surfaces," Oxford Univ. Press, 1941, 3rd edtn., p. 136) and from other soluble alcohols

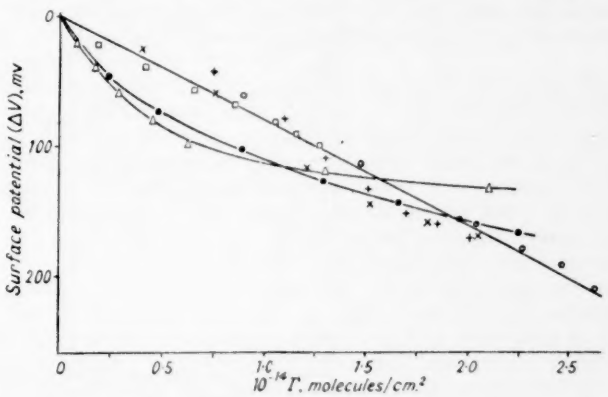


FIG. 1.

□ □ Ethyl alcohol.
× × *n*-Propyl alcohol.
○ ○ *n*-Butyl alcohol.
+ + *n*-Amyl alcohol.
● ● *n*-Hexyl alcohol.
△ △ *n*-Decyl alcohol.

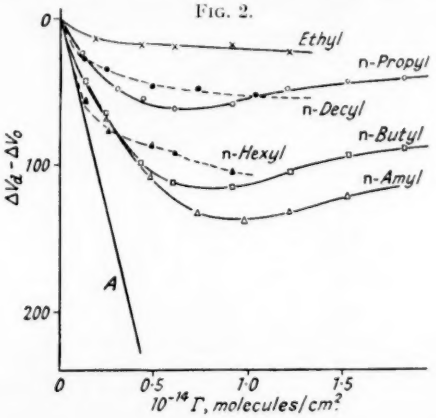
(Sawai, *Trans. Faraday Soc.*, 1935, **31**, 765). For these shorter-chain alcohols in the very dilute concentrations employed, the orientation of the polar group with respect to the liquid surface is little influenced by variation in chain length. The points for hexyl alcohol lie on a curve which deviates somewhat from the straight line. Similar deviations were observed by Posner and Alexander (*Trans. Faraday Soc.*, 1949, **45**, 651) for *sec.*-octyl alcohol; the best straight line through the available experimental points gave 226 mD. The decyl alcohol curve (Fig. 1) shows that this deviation increases with increasing chain length. Posner and Alexander (*loc. cit.*) determined Γ values from Gibbs's equation, and also from the equation of state $\pi\ (A - A_0) = xkT$ (where π is the surface pressure, A_0 is constant for a given homologous series, and x is specific to the solute) and obtained points lying above the standard line at the lower concentrations. It is presumably for this reason that these authors treated the deviations observed at lower concentrations as dependent upon the method used in calculating Γ rather than as representing a true molecular property. However, the additional evidence obtained in this work justifies a reconsideration of these deviations. Previous parts in this series (*e.g.*, Part XIV, *J.*, 1949, 3406) have shown that the behaviour of decyl alcohol follows closely that predicted by calculations based upon the applicability of Gibbs's equation. For this reason, the values derived from Gibbs's equation are preferred to those calculated from the equation of state, and the deviations observed at chain lengths of C_6 and above are considered to represent a real surface property of the molecules concerned. The initial slopes of the ΔV–Γ curves for hexyl and decyl alcohols give μ values of about 560 and 640 mD, respectively. If the

addition of carbon atoms beyond C_5 involved no more than the lengthening of a straight chain, there is no apparent reason why the orientation of the dipole with respect to the surface should change, since the chains are regarded as lying flat on the surface in these very low concentrations. The reason is perhaps to be found in the variation in the shape assumed by the carbon chain with increasing chain length. From a study of the physical properties of the hydrocarbons, Ward (*Trans. Faraday Soc.*, 1946, **42**, 399) noted that above C_8 the addition of each CH_2 group causes a constant increase in the molecular volume and surface area; below C_8 the same regularity does not occur. It is clear from Fig. 1 that at about C_6 some change in the equilibrium shape or position of the adsorbed molecule occurs which is sufficient to change the surface orientation of the polar group.

As concentration increases, the slope of the curves for hexyl and decyl alcohol (and thus μ) decreases. The concentration values given on p. 1160 are equivalent to Γ values of $1{\cdot}6 \times 10^{14}$ and $0{\cdot}65 \times 10^{14}$ molecules/cm.^{2} for hexyl and decyl alcohols, respectively, and in consequence mutual interference occurs within the Γ range studied. This must necessarily result in a mean position of orientation differing from that taken up by an independent molecule, and a consequent alteration in the orientation of the dipole.

Disorientation Surface Potentials.—Disorientation potentials (ΔV_d) are listed in Table 1; the effect of disorientation of the surface film is considerable, and persists down

FIG. 2.



to ethyl alcohol. Even with methyl alcohol a slight disorientation effect was observed, of the order of a few mv. Values of $\Delta V_d - \Delta V_0$, which represent directly the effect of disorientation, are plotted against Γ in Fig. 2. The curves show two important features: (*a*) The values of $\Delta V_d - \Delta V_0$ increase with increasing chain length up to C_5; thereafter, the disorientation effect diminishes, and the values of $\Delta V_d - \Delta V_0$ diminish with increasing chain length. (*b*) For any given alcohol, the $\Delta V_d - \Delta V_0$ values rapidly level off with increasing Γ.

Concerning (*a*), dipole-moment values calculated from surface-potential measurements are rarely greater than a quarter of the values for molecules containing the same end groups measured by the ordinary methods (Adam, *op. cit.*, p. 38; Frumkin and Williams, *Proc. Nat. Acad. Sci.*, 1929, **15**, 400). For the aliphatic alcohols, μ is about 1700 mD. The low measured values of μ arise partly from the fact that in the application of Helmholtz's equation the dielectric constant cannot be considered as unity (Rideal and Bosworth, *Physica*, 1937, **4**, 925), and partly from the orientation of the adsorbed dipoles at angles of other than 90° to the liquid surface. If we ignore the dielectric considerations, the necessary values of $\Delta V_d - \Delta V_0$ which would be required to augment the 223 mD value to the full value of 1700 mD, would lie along the line *A* shown in Fig. 2. Such values are not obtained experimentally, although as chain length increases up to C_6, the curves approach line *A* asymptotically at very low concentrations. The results may be interpreted satisfactorily if we consider that the disorientation of adsorbed molecules also involves

simultaneous disorientation of water molecules in the surface of the solution. It is reasonable to suppose that, for a given surface excess, the longer the chain length of a molecule arriving at the surface the greater is the number of water molecules undergoing temporary (kinetic) disorientation; each disoriented water molecule will make its contribution to the measured value of $\Delta V_d - \Delta V_0$. The combined effect of tilt and water disorientation appears to reach a maximum at about C_5. Although the disorientation of water molecules continues to increase with chain length, it becomes more difficult to alter the angle of tilt of the longer chains; the latter factor outweighs the former beyond C_5, so that $\Delta V_d - \Delta V_0$ then decreases with increasing chain length.

Feature (*b*) (above) is common to all curves. When mutual interference of adsorbed molecules occurs (which is the case over the Γ range studied), the values of $\Delta V_d - \Delta V_0$ should be proportional to Γ, whereas the experimental curves show departure from such linearity. Under these conditions this cannot be the result of change in Γ *per se*, but results rather from change in the velocity of arrival of adsorbing alcohol molecules at the surface, which is known (Part V, *J.*, 1945, 354) to diminish with increasing bulk concentration. It is feasible that the variation in angle of tilt from the equilibrium angle, and also the extent to which the water molecules in the surface undergo temporary kinetic disorientation, should both become less pronounced when the adsorbing molecules arrive more slowly at the surface. This change in adsorbing velocity provides a suitable explanation for the departure of the $(\Delta V_d - \Delta V_0)$-$\Gamma$ curves from linearity, and also for the minima which occur in some of the curves.

Adsorption to an Equilibrium Film.—When Γ in the equilibrium film is sufficiently large for mutual interference of adsorbed molecules to occur, it is to be expected that the arrival of additional adsorbate will give rise to a potential representing disorientation of the newly arrived molecules ($\Delta\Gamma$), together with the partial disorientation of some, or all, of the molecules already adsorbed and at equilibrium orientation. Even at Γ values a little below that required for mutual interference, newly arriving molecules are likely to strike many of those already adsorbed, again giving rise to a disorientation potential greater than that equivalent to $\Delta\Gamma$. This condition applied to the most dilute solutions of decyl alcohol considered in Part XVIII (*loc. cit.*). In contrast, at small Γ values the newly arriving molecules are unlikely to strike those already adsorbed, and the disorientation potential obtained on successive additions of solute should be no more than that equivalent to the $\Delta\Gamma$ value resulting from each addition. These limiting conditions are typical of dilute solutions of solutes of low surface activity, and are illustrated by the results in Fig. 3. Fig. 3(*a*) shows the changes occurring when *n*-propyl alcohol is added in successive stages to the solution in the trough, and the relevant concentrations are given in Table 2(*a*).

TABLE 2.

Addition number	Trough concn., %	$10^{-14}\Delta\Gamma$, molecules/cm.^{2}	$\Delta V_d - \Delta V_0$ (from first additions)	$\Delta V_d - \Delta V_0$ (from successive additions)
(*a*) *n*-Propyl alcohol.				
—	0·0			
1	0·154	0·533	63	—
2	0·302	0·4	57	52
3	0·444	0·275	50	45
4	0·581	0·255	44	36
5	0·713	0·2	36	30
6	0·840	0·165	32	28
7	0·960	0·12	26	26
8	1·076	0·09	22	22
(*b*) *n*-Hexyl alcohol.				
—	0·0			
1	0·019	1·37	103	—
2	0·038	1·225	100	90
3	0·057	0·985	93	74

Col. 3 shows the increment in Γ resulting from each addition, and col. 4 the influence of disorientation on the potential values, it being assumed that in each case the quantity $\Delta\Gamma$ was adsorbed to a clean water surface. The agreement between the values in cols. 4 and 5 is sufficiently close to indicate that under these conditions the disorientation potential

values represent disorientation of the incremental surface excess $\Delta\Gamma$ only, and that the molecules already adsorbed undergo no disturbance as a result of the further adsorption.

Some departure from these limiting conditions is observed with increase in chain length. With butyl alcohol solutions, for example, the successive disorientation potentials are appreciably greater than those equivalent to $\Delta\Gamma$ only. Further increase in the chain length brings the concentration required to give mutual interference in the surface within the experimental concentration range. The results obtained on successive addition of *n*-hexyl alcohol [Fig. 3(*b*)] illustrate the effect. Cols. 4 and 5, Table 2(*b*), show that the observed disorientation potentials are now less than those corresponding to full disorientation of $\Delta\Gamma$, and the effect is observed to a more pronounced degree with the concentrated *n*-decyl alcohol solutions discussed in Part XVIII (*loc. cit.*).

Rate of Reorientation.—One of the most curious features observed in this work is the very slow rate at which the disoriented film undergoes reorientation. Typical curves, collected in Fig. 4, show that the time required for orientation diminishes as chain length is decreased. Because of the practical limitations of the apparatus it is difficult to determine the true orientation times in the case of butyl and lower alcohols, but they are

FIG. 3.

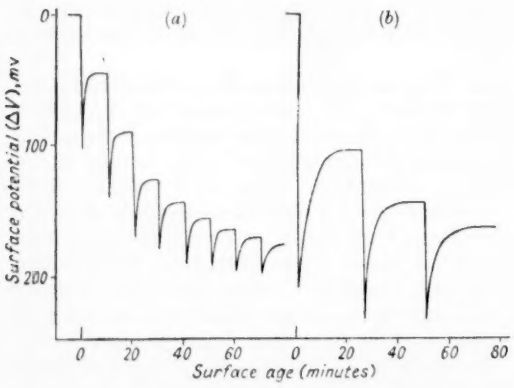
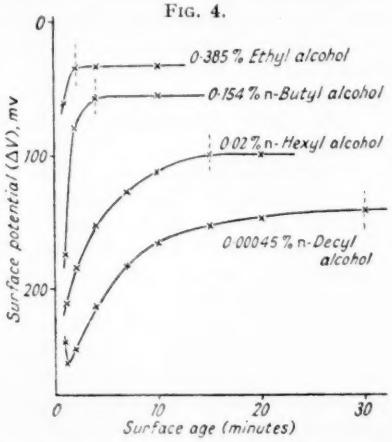


FIG. 4.



of an entirely different order from those required for initial adsorption. If the alcohol molecules, and some of the water molecules, present in the surface when the film is first formed, are regarded as merely displaced from their equilibrium position, then it would be expected that normal kinetic agitation would re-establish the equilibrium orientation almost instantly. Since reorientation occurs after the establishment of the adsorbed film, no considerations involving the surface-energy barrier (be it electrical or kinetic) are likely to be applicable. It seems more probable that reorientation involves the breaking of some form of chemical bond. If strong hydrogen bonding at the surface exists, then reorientation of both alcohol and water molecules may involve the breaking of some of these bonds and the re-forming of others. A less attractive possibility is that the initial adsorbed film is not homogeneous and that during reorientation associated molecules become separated to give a truly gaseous film.

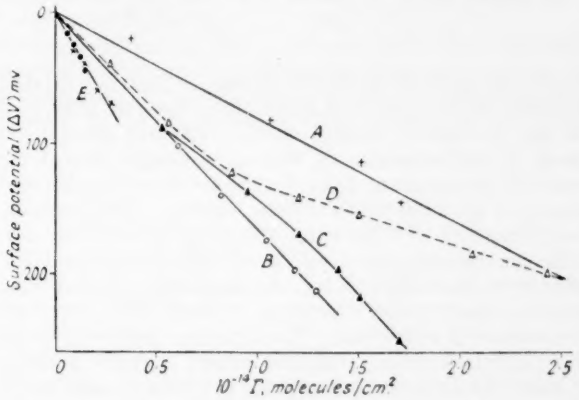
Influence of Chain Structure.—The influence of chain structure on surface potentials has been studied with reference to the isomers of butyl and amyl alcohol. Attention has been directed in particular to the influence of chain structure on the apparent dipole moment of the molecule. Tables 3 and 4 give surface-tension and surface-potential data respectively for three of the alcohols studied.

tert.-*Butyl Alcohol.*—The ΔV_0–Γ points for this alcohol lie on a straight line (*B*, Fig. 5) passing through the origin. The slope is much greater than that for the normal alcohol (line *A*) and corresponds to $\mu = 460$ mD. There are features in the structure, $CMe_3{\cdot}OH$, which give it a particular significance. With the straight-chain alcohols, free rotation

round the several available bonds precludes a rigid derivation of the vertical components of the dipoles concerned. In calculations of the effective vertical component for long-chain carboxylic acids, Adam and Harding (*Proc. Roy. Soc.*, 1932, *A*, **138**, 411) pointed out the hypothetical nature of the assumptions it was necessary to make concerning the distribution of the C, H, and O atoms of the polar group. With *tert.*-butyl alcohol, three CH_3 groups are disposed symmetrically round the C–O bond; this symmetry renders it

FIG. 5.

+ + *iso*Butyl alcohol.
○ ○ *tert.*-Butyl alcohol.
△ △ *iso*Amyl alcohol.
▲ ▲ *tert.*-Amyl alcohol.
● ● Ethylene glycol.
× × Butane-1 : 3-diol.



highly probable that the molecule will be orientated with the C–O bond vertical to the surface as shown below, since the only forces determining orientation in this case arise from the hydrophilic character of the OH group. Free rotation round the C–O bond, or around any of the three CH_3–C bonds, does not disturb the symmetry. Again, free rotation of the H atom round the C–O bond as illustrated does not alter the direction of the O–H dipole to the surface. This is therefore one of the few cases where comparison of the observed

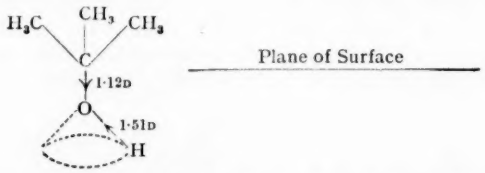
TABLE 3.

Concn., %	d_4^{16}	γ, dynes/cm.	Γ, g. $\times 10^{-8}$/cm.²	Concn., %	d_4^{16}	γ, dynes/cm.	Γ, g. $\times 10^{-8}$/cm.²
			tert.-Butyl alcohol.				
8·22	0·9856	36·55, 36·75	—	0·150	—	65·8, 66·0	1·20
2·05	0·9959	49·85, 49·75	3·35	0·075	—	68·15, 68·35	0·96
0·600	0·9990	59·6, 59·6	1·94	0·0375	—	70·15, 70·15	0·72
0·300	—	62·65, 62·8	1·50				
			*iso*Butyl alcohol				
5·04	0·9931	32·95, 32·95	6·04	0·315	—	58·65, 58·9	1·73
2·52	0·9964	40·7, 40·7	4·00	0·157	—	63·2, 63·2	1·54
1·26	0·9983	48·05, 48·1	3·00	0·079	—	64·8, 64·8	1·14
0·630	0·9992	53·6, 53·7	2·43	0·039	—	67·5, 67·5	0·72
			tert.-Amyl alcohol				
5·33	0·9931	35·30, 35·50	—	0·133	—	65·0, 65·1	1·60
1·33	0·9981	49·25, 49·15	3·00	0·067	—	67·25, 67·3	1·10
0·53	0·9992	56·3, 56·6	2·55	0·0335	—	70·0, 70·1	0·55
0·266	—	61·2, 61·25	2·14				

TABLE 4.

tert.-Butyl alcohol			*iso*Butyl alcohol			*tert.*-Amyl alcohol		
C, %	ΔV_0	ΔV_d	C, %	ΔV_0	ΔV_d	C, %	ΔV_0	ΔV_d
0·025	62	130	0·031	20	96	0·0246	52	148
0·048	100	—	0·123	83	200	0·0485	98	—
0·071	116	160	0·242	114	—	0·0716	116	—
0·095	140	—	0·358	146	—	0·0940	136	—
0·116	152	178				0·123	152	200
0·246	188	208				0·242	214	—
0·358	208	216				0·358	246	—
0·470	230	235						

dipole with the dipole found by other methods may be made without the uncertainty usually associated with angle of tilt of the dipole.



The dipole moment for the O–H bond is 1510 mD (Syrkin and Dyatkina, " Structure of Molecules and the Chemical Bond," Butterworth, 1950, p. 206); that for the C–O bond will be near its value in methyl alcohol (1120 mD), since the total moments of methyl and *tert.*-butyl alcohol molecules are 1690 and 1650 mD, respectively. On using these values, it is found that the resultant dipole for the *tert.*-butyl alcohol molecule under these conditions is inclined at an angle of 63° to the vertical. The vertical component of the dipole is 750 mD, compared with the value 460 mD obtained from surface-potential measurements. The difference between these two values represents the real discrepancy between the μ value obtained from measurements by other methods, and that obtained by direct application of Helmholtz's equation $\Delta V = 4\pi n\mu$, particularly since the present system is not complicated by the presence of added ions. The difference between calculated and observed values of μ for an equilibrium surface will arise largely from the permanent change in orientation of water molecules brought about by the presence of adsorbed alcohol molecules in the film. This effect may be expressed quantitatively in terms of the dielectric constant ε, where $\mu\varepsilon = \bar{\mu}\cos\theta$ (Adam, *op. cit.*, p. 38); $\bar{\mu}\cos\theta$ is 750 mD, whence $\varepsilon = 1{\cdot}63$.

It is now possible to determine with some degree of accuracy the angle of tilt of the dipole for the straight-chain alcohols up to C_5, provided that it can be assumed that this value of ε does not vary appreciably with the length and structure of the carbon chain. This assumption is reasonable, since the polar group, rather than the carbon chain, will be responsible for the rearrangement of the water molecules. (This water disorientation is distinct from that caused at the non-equilibrium surfaces discussed in connection with Fig. 2, where the temporary water disorientation is kinetic rather than electrical in origin.) Again, the ΔV_0–Γ points for the C_2—C_5 alcohols all lie along a single line (Fig. 5); it follows that if ε was not constant, the change in ε would be balanced exactly by a corresponding change in the angle of tilt with chain length, which is most improbable. Therefore the unique feature of the *tert.*-butyl alcohol molecule lies solely in its vertical orientation, and there is no reason to suppose that the value of ε determined with this alcohol should differ from that operating in the straight-chain alcohol films. The values for the total dipole moment $\bar{\mu}$ of the C_2—C_5 alcohols are 1·70, 1·64, 1·66, 1·65, respectively (Syrkin and Dyatkina, *op. cit.*, p. 215). Substituting the mean value into expression

$$\Delta V_0/n = (4\pi\bar{\mu}\cos\theta)/\varepsilon$$

where $\Delta V_0/n$ is the slope of line *A*, Fig. 5, we find that θ, the inclination of the dipole to the vertical, is 78°, compared with 63° for *tert.*-butyl alcohol.

iso*Butyl Alcohol.*—The ΔV_0–Γ points for this alcohol are given in Fig. 5 and are seen to lie very close to line *A* which is standard for the normal alcohol. It is consistent with the above treatment that the inclination of the dipole in a molecule having the structure $CHMe_2{\cdot}CH_2{\cdot}OH$ should agree with that of the straight-chain alcohol rather than with the symmetrical *tert.*-butyl isomer.

tert.-*Amyl Alcohol.*—Curve *C*, Fig. 5 (almost a straight line), shows the ΔV_0–Γ relationship for this alcohol. The slope of a straight line drawn through the points is a little less than for *tert.*-butyl alcohol, corresponding to $\mu = 405$ mD, and the dipole is inclined at an angle of 66° to the vertical. *tert.*-Butyl alcohol being considered as standard, the extent to which the dipole of similar molecules will deviate from an angle of 63° to the vertical will depend upon the extent to which substitution of the CH_3 groups introduces dissymmetry round the C–O bond. The substitution of one CH_3 group by a C_2H_5 group (as in *tert.*-

amyl alcohol) introduces a relatively small degree of dissymmetry. The surface orientation therefore resembles that of *tert.*-butyl alcohol, except that the dipole undergoes a small further tilt from 63° to 66°. If two CH_3 groups in *tert.*-butyl alcohol are replaced by H atoms, the symmetry is destroyed to such an extent that the dipole takes up the 78° position typical of straight-chain alcohols.

iso*Amyl Alcohol.*—The behaviour of this alcohol is somewhat anomalous. Analogy with the results discussed above would suggest that the ΔV_0–Γ points should lie along line *A*, Fig. 5, but this is the case at the higher concentrations only (curve *D*).

Surface Potentials of Solutions of Dihydric Alcohols.—For comparison with the behaviour of the monohydric alcohols given above, the surface potentials of aqueous solutions of two dihydric alcohols have been measured, and the results, together with surface tension data, are given in Table 5. The ΔV_0–Γ points for the two glycols lie close to a common line (*E*, Fig. 5).

TABLE 5.

Concn., %	γ, dynes/cm.	$10^{-14}\,\Gamma$, molecules/cm.^{2}	ΔV_0	ΔV_0 †	μ, mD	Concn., %	γ, dynes/cm.	$10^{-14}\,\Gamma$, molecules/cm.^{2}	ΔV_0	ΔV_0 †	μ, mD
Ethylene glycol.						*Butane*-1 : 3-*diol.*					
0·0	72·5	—	—	—	—	0·18	—	0·083	25	—	880
0·19	—	—	8	—	—	0·36	—	0·15	40	—	840
0·38	72·2	0·065	15	—	830	0·53	70·3	0·22	59	—	820
0·388	—	—	—	5	—	0·70	69·8	0·275	71	—	750
0·55	—	0·10	24	—	830	1·12	68·8	—	—	—	—
0·73	—	0·12	34	—	840	2·24	66·3	—	—	—	—
0·775	—	—	—	9	—	4·48	62·0	—	—	—	—
0·89	71·9	0·15	44	—	890	8·96	56·5	—	—	—	—
3·00	70·6	—	—	—	—						
3·10	—	—	—	46	—						
5·63	69·1	—	—	—	—						
6·2	—	—	—	96	—						
11·25	67·3	—	—	—	—						
12·4	—	—	—	127	—						

† Results of Frumkin, Donde, and Kulverskaya (*Z. physikal. Chem.*, 1926, **123**, 321).

The surface-tension values for ethylene glycol solutions agree closely with values reported by Frumkin, Donde, and Kulverskaya (*loc. cit.*) but the value of ΔV_0 determined in this work are greater than theirs. This may arise from the fluctuating nature of the potentials observed for these solutions. Although the air electrode was stationary, no truly steady state was reached with solutions of these two dihydric alcohols. The surface film behaved as though it was heterogeneous, and each of the ΔV_0 results given above is the mean of a series of fluctuating values. Nevertheless, the range of fluctuation was sufficiently narrow to indicate a real disagreement between the two sets of results. In no case was any significant disorientation potential observed on addition of the glycols to the trough, so the presence of a hydrophilic group at each end of the molecule serves to ensure its immediate orientation on arrival at the surface. The values of μ for each alcohol, determined directly from Helmholtz's equation, are given in Table 5. The close agreement indicates that the angle of tilt of the dipoles in these two glycols is not appreciably influenced by surface excess, or by alteration from 2 to 3 in the number of carbon atoms separating the polar groups; neither does it appear necessary for this constant angle of tilt that the polar groups should be in terminal positions in the chain. If the two dipoles are considered to make separate contributions to the surface potential, the value for each (about 424 mD) might be expected to lie between the minimum and maximum values observed for monohydric alcohols (Fig. 5), and this is in fact the case. However, it is inadvisable to employ this value in the calculation of angle of tilt of each dipole, in view of the possible influence of one dipole on the other which may result from their close proximity.

The authors are indebted to the Department of Scientific and Industrial Research for a Maintenance Grant to one of them (D. L.) during the work recorded in this and the preceding three papers.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 30th*, 1952.]

233. *Determination of Electrokinetic Charge and Potential by the Sedimentation Method. Part III.* Silica in Some Aqueous Chloride Solutions.*

By C. I. Dulin and G. A. H. Elton.

The sedimentation method is used to determine the electrokinetic charges and potentials of fused silica surfaces in dilute aqueous solutions of various chlorides. Although the results for potassium chloride agree well with those obtained from streaming-potential measurements, yet those for chlorides with higher-valency cations differ to some extent. Possible reasons for these deviations are discussed.

The sedimentation method (Elton, *Proc. Roy. Soc.*, 1949, A, **197**, 568; *J. Chem. Physics*, 1951, **13**, 1317; Dulin and Elton, Part I;* Elton and Hirschler, Part II *) enables the calculation of the electrokinetic charge from the velocity of sedimentation of a suspension of small particles from the expression

$$\sigma^2 = (u_0 - u)\boldsymbol{g}\kappa(\rho_2 - \rho_1)/MA_0^2uu_0\rho_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where σ is the net charge per unit area in the diffuse part of the double layer at the particle–liquid interface, $\boldsymbol{g}$ the gravitational constant, κ the specific conductivity of the suspension, u_0 the rate of settling of the suspension in the absence of electroviscosity (*i.e.*, in a concentrated electrolyte solution), u the analogous rate in the given solution, ρ_1 and ρ_2 are the densities of solution and particle respectively, M is the mass of particles per ml. of suspension, and A_0 the area per g. of the particles.

Once this charge has been obtained, the electrokinetic potential ζ may be determined for binary electrolyte solutions of normality c from the expression

$$\sigma = \left(\frac{N\varepsilon\boldsymbol{k}Tc}{2\pi}\right)^{\frac{1}{2}}\left\{\frac{1}{z_-}[\exp(z_-\boldsymbol{e}\zeta/\boldsymbol{k}T) - 1] + \frac{1}{z_+}[\exp(-z_+\boldsymbol{e}\zeta/\boldsymbol{k}T) - 1]\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad 2)$$

given by Verwey and Overbeek ("Theory of the Stability of Lyophobic Colloids," 1948, Elsevier Publ. Co., Inc., London). In equation (2), $\boldsymbol{N}$ is the Avogadro number, ε the dielectric constant in the double layer, $\boldsymbol{k}$ the Boltzmann constant, T the absolute temperature, z_+ and z_- are the valencies of cation and anion respectively, and $\boldsymbol{e}$ is the charge on the electron.

For solutions containing more than two ionic species, a more complicated expression has to be used, *viz.*

$$\sigma = \left(\frac{N\varepsilon\boldsymbol{k}T}{2\pi}\right)^{\frac{1}{2}}\left\{\Sigma\frac{c_r}{z_r}[\exp(z_r\boldsymbol{e}\zeta/\boldsymbol{k}T) - 1] + \Sigma\frac{c_s}{z_s}[\exp(-z_s\boldsymbol{e}\zeta/\boldsymbol{k}T) - 1]\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad (3)$$

where the summation terms are those of the negative and positive ions respectively, c_r and c_s are the normalities of the ions of valency $(z_r)_-$ and $(z_s)_+$, respectively.

In solutions of chlorides of the higher-valency metals, hydrolysis often occurs, especially in very dilute solutions, resulting in the removal of multivalent cations and their replacement by an equivalent number of hydrogen ions. In calculating the electrokinetic potential from the charge, this fact must be taken into account. If the charge and potential are positive, the positive-ion summation term in equation (3) is negligible, except for very low values of ζ. Consequently, the effect of hydrolysis on the calculated value of the potential is generally small in cases where the charge is positive. For negative charges and potentials, however, the positive-ion summation term in (3) is the more important, and changes in electrolyte concentration produced by hydrolysis are important, and must be allowed for so far as is possible. It may be said, in general, that for a given surface charge, the behaviour of the counter-ions is the important factor in determining the electrokinetic potential.

Measurements were made of the sedimentation velocities of homodisperse suspensions of fused silica powder in dilute aqueous solutions of chlorides of sodium, hydrogen, barium,

* Part I, *J.*, 1952, 286; Part II, *J.*, 1952, 2953.

magnesium, lanthanum, and thorium, data from smoothed velocity–concentration curves being taken for the calculation of charges and potentials. The tables give the results obtained for these solutions (three in detail), some of which have been studied by Jones and

Summary of results for all solutions.

	σ, e.s.u./cm.²						ζ, mv					
c	NaCl	HCl	$BaCl_2$	$MgCl_2$	$LaCl_3$	$ThCl_4$	NaCl	HCl	$BaCl_2$	$MgCl_2$	$LaCl_3$	$ThCl_4$
2×10^{-3}	5289	4434	—	—	3342*	—	100·0	91·3	—	—	77·0*	—
1×10^{-3}	4331	3493	887	—	472*	3142*	106·2	96·6	25·9	—	18·0*	90·8*
5×10^{-4}	3470	2781	1034	345	0	3876*	113·7	102·5	36·2	16·2	0·0	119·1*
2×10^{-4}	2528	2090	1132	745	361	2066*	121·8	112·0	49·2	39·2	19·4	118·3*
1×10^{-4}	1990	1689	1082	809	496	1229*	126·5	117·9	59·5	49·4	28·4	105·0*
5×10^{-5}	1581	1379	922	784	530	723*	132·2	125·3	61·3	57·2	36·5	92·3*
2×10^{-5}	1201	1096	791	718	467	327*	141·6	137·0	72·0	66·6	42·5	75·8*
1×10^{-5}	1040	991	674	639	441	159*	151·8	143·8	74·4	72·4	47·8	58·1*
5×10^{-6}	—	—	600	596	447	47*	—	—	79·8	79·6	54·6	24·6*
2×10^{-6}	—	—	553	552	477	96	—	—	89·5	89·4	63·7	26·8
1×10^{-6}	—	—	548	563	—	333	—	—	98·2	98·9	—	46·4

All values are negative except those marked *.

c	$u \times 10^3$, cm./sec.	$10^6\kappa$	σ, e.s.u./cm.²	ζ, mv	ζ Wood,* interp'd	*c*	$u \times 10^3$, cm./sec.	$10^6\kappa$	σ, e.s.u./cm.²	ζ, mv	ζ Wood,* interp'd
Results for $BaCl_2$.											
1×10^{-3}	$2{\cdot}88_6$	136·0	−887	−25·9	−45·0	2×10^{-5}	$2{\cdot}39_2$	3·66	−791	−72·0	−98·0
5×10^{-4}	$2{\cdot}88_0$	67·11	−1034	−36·2	−58·0	1×10^{-5}	$2{\cdot}30_0$	2·16	−674	−74·4	−103·5
2×10^{-4}	$2{\cdot}74_7$	27·68	−1132	−49·2	−70·0	5×10^{-6}	$2{\cdot}22_0$	1·58	−600	−79·8	−109·0
1×10^{-4}	$2{\cdot}64_3$	14·73	−1082	−59·5	−79·0	2×10^{-6}	$2{\cdot}13_1$	1·05	−553	−89·5	−120·0
5×10^{-5}	$2{\cdot}53_2$	7·21	−922	−61·3	−88·0	1×10^{-6}	$2{\cdot}08_0$	0·95	−548	−98·2	—
Results for $LaCl_3$.											
2×10^{-3}	$2{\cdot}88_2$	323·60	+3342	+77·0	—	5×10^{-5}	$2{\cdot}79_4$	8·71	−530	−36·5	−27·0
1×10^{-3}	$2{\cdot}90_2$	162·20	+472	+18·0	+12·5	2×10^{-5}	$2{\cdot}69_0$	3·39	−467	−42·5	—
5×10^{-4}	$2{\cdot}90_7$	75·86	0	0	−7·5	1×10^{-5}	$2{\cdot}59_1$	2·00	−441	−47·8	—
2×10^{-4}	$2{\cdot}89_2$	31·62	−361	−19·4	−16·0	5×10^{-6}	$2{\cdot}47_8$	1·45	−447	−54·6	—
1×10^{-4}	$2{\cdot}85_5$	16·98	−496	−28·4	−22·0	2×10^{-6}	$2{\cdot}17_6$	0·87	−477	−63·7	—
Results for $ThCl_4$.											
1×10^{-3}	$2{\cdot}74_6$	208·90	+3142	+90·8	+141·0	2×10^{-5}	$2{\cdot}84_2$	5·89	+327	+75·8	+126·0
5×10^{-4}	$2{\cdot}48_0$	109·60	+3876	+119·1	+158·0	1×10^{-5}	$2{\cdot}87_8$	3·16	+159	+58·1	+96·0
2×10^{-4}	$2{\cdot}61_4$	47·86	+2066	+118·3	+175·0	5×10^{-6}	$2{\cdot}90_3$	2·04	+47	+24·6	+57·5
1×10^{-4}	$2{\cdot}70_7$	25·70	+1229	+105·0	+177·0	2×10^{-6}	$2{\cdot}88_2$	1·38	−96	−26·8	—
5×10^{-5}	$2{\cdot}77_5$	13·80	+723	+92·3	+164·0	1×10^{-6}	$2{\cdot}61_2$	1·23	−333	−46·4	—

* Interpolated from Wood's data (*loc. cit.*).

Wood (*J. Chem. Physics*, 1945, **13**, 106) and by Wood and Robinson (*ibid.*, 1946, **14**, 258; *J. Amer. Chem. Soc.*, 1947, **69**, 1862), using in each case the streaming-potential method. Most of the measurements of these workers involved the use of silver–silver chloride reversible electrodes, a fact which produced errors of a few millivolts in their results (see Part I), owing to contamination of the solution by traces of electrolyte leached from the electrodes.

In order to verify that the results obtained by the sedimentation method were independent of particle size and suspension concentration over the range used (already verified for glass particles, see Part I, *loc. cit.*), measurements were made on two widely different suspensions in dilute hydrochloric acid, the final values of ζ obtained being in agreement to within about one millivolt at all electrolyte concentrations studied. This confirms that in our experiments, using suspensions with volume fractions of solid of the order of 10^{-3} to 10^{-4}, particle–particle interaction is negligible (see also Oseen, *Ark. Mat. Astron. och. Fysik*, 1911, **7**, 33; Faxen, *ibid.*, 1925—1927, **19**, *a*, 13; Smoluchowski, *Bull. Acad. Sci. Cracovie*, 1911, **1**, *a*, 28; Stimson and Jeffrey, *Proc. Roy. Soc.*, 1926, *A*, **111**, 110). In view of this finding, measurements on the other chloride solutions were made on a single suspension, at least two runs being made at each concentration.

Discussion.—It is seen that the results for sodium chloride solutions are closely similar to those obtained previously for potassium chloride, the difference in charge being small,

and in potential negligible. The fact that the nature of the univalent cation has little effect on the electrokinetic properties indicates that they probably possess rather low specific chemical adsorption potentials at the interface, and play only a small part in the construction of the fixed part of the double layer.

With hydrogen chloride solutions, however, the charge is lower throughout, the difference being fairly constant and of the order 400—700 e.s.u. over a wide range. A difference is to be expected, since in the salt solutions there occurs adsorption into the fixed part of the double layer of hydroxyl and, more important, bicarbonate ions from the conductivity water, whilst in acid solutions these foreign ions will be very largely suppressed, giving a negative charge in the fixed part of the double layer due almost entirely to chloride ions. The difference between the charge in sodium or potassium chloride solutions and that in hydrogen chloride will probably be about equal to the charge carried by silica in the pure solvent, it being assumed that the charges are approximately additive. By extrapolating results to high dilution, a value of the charge in equilibrium water of about 530—550 e.s.u. has been obtained, in agreement with the observed difference between the charge in the salt and in acid solutions. At very low concentrations the difference becomes rather smaller as the degree of suppression of the bicarbonate ions decreases. The effect occurs at a slightly higher concentration than would be expected on this basis alone, possibly indicating that the assumption that the charges are additive is only valid approximately in this range.

For both magnesium and barium chloride solutions the charges and potentials are lower than for the chlorides of univalent cations, owing to the increased ease with which the bivalent cations are taken into the fixed part of the double layer. The charges and potentials for the magnesium chloride solutions are somewhat lower than for barium chloride, especially at the higher concentrations. The accuracy of the measurements is lower for these concentrations, owing to electroviscosity being rather small, and the sedimentation meniscus less sharp, but the differences are considerably greater than the experimental error. This presumably indicates that the specific chemical adsorption potential of the magnesium ion is significantly greater than that of the barium ion, so that magnesium ions are more easily adsorbed into the fixed part of the double layer, with a consequent lowering of charge and potential. The values of ζ obtained by us for barium chloride are lower by about 20% than those of Wood and Robinson (*loc. cit.*). This discrepancy is considerably greater than that found for potassium chloride, where the difference between the results from the two methods was never greater than 5%, after allowance for the effect of contamination of the solutions by leaching fron the electrodes in the streaming-potential measurements. Some possible reasons for the observed difference are discussed below.

Preferential adsorption of a high-valent cation into the fixed layer is shown to a greater extent by lanthanum chloride, for which the charge reaches zero at a concentration of 5×10^{-4}N, becoming positive at higher concentrations. The values of ζ are small throughout the range studied and differ by only a few mv from those of Wood and Robinson (*loc. cit.*). Corrections for the change in concentration brought about by hydrolysis were made in calculating ζ from equation (3).

Thorium chloride shows a negative charge and potential at very high dilutions, reaching zero at a concentration of about $3—4 \times 10^{-6}$N, and becoming positive at higher concentrations. The positive charge rises to a maximum value at a concentration of about 4×10^{-4}N, then falls away towards zero. The velocity–concentration curve is of rather complicated shape for thorium chloride. As the concentration is lowered from high values, the velocity falls from its limiting value, reaching a minimum at the concentration of maximum charge. The velocity then rises to the limiting value again, passing through a maximum at the concentration of zero charge, then decreasing again fairly sharply. Once again, allowance had to be made for the effect of hydrolysis in calculating ζ from equation (3). The results obtained show the same trends with concentration as those of Wood and Robinson, but the quantitative agreement is not good, differences in ζ of up to 35% being found.

Various possible causes of the observed differences in solutions of chlorides of the multivalent metals may be considered. First, contamination of the solutions by silver

chloride from the electrodes in the streaming-potential experiments can produce errors of 20 mv or even more in very dilute solutions (see Part I, *loc. cit.*), but the dissociation of the silver chloride should be largely suppressed at concentrations much above 10^{-5}N, and, furthermore, this contamination would probably bring about a lowering of ζ, while in practice the streaming-potential results are generally found to be rather higher than those for sedimentation velocity.

In calculating ζ from experimental results, the dielectric constant in the diffuse part of the double layer is involved (see Part I). It is known that the value of ε in this layer may differ considerably from that of the bulk solution (see Conway, Bockris, and Ammar, *Trans. Faraday Soc.*, 1951, **47**, 756). In the streaming potential equation

$$\zeta = -4\pi\eta E\kappa/\varepsilon P \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where η is the viscosity of the solution, P the applied pressure, and E the streaming potential, the value of ζ obtained from a given set of experimental data depends linearly on ε, while in calculations of ζ from equation (3) for sedimentation experiments ε is involved logarithmically. If the bulk value of the dielectric constant is used in each case, therefore, the two sets of results for ζ will differ if this value is the incorrect one for use in the double layer. The fact that the two sets agree quite well for a uni-univalent electrolyte therefore appears to indicate that the appropriate mean value for ε in the diffuse layer in this case is not far different from the bulk value for potentials of this magnitude. Bigger deviations from the bulk value, are, however to be expected in solutions containing multivalent cations (Conway, Bockris, and Ammar, *loc. cit.*), but a simple calculation shows that this should produce lower values of ζ by the streaming-potential method, while in fact the reverse is the case.

It appears most probable that the difference arises from the difficulty in assessing accurately the concentration of each ionic species in a solution of a multivalent metal chloride. In addition to hydrolysis direct to undissociated base with consequent liberation of hydrogen ions, which can be allowed for in terms of the known dissociation constant of the base, other products of partial and complete hydrolysis will be formed. For example, in the case of thorium chloride various partially hydrolysed ions will exist, *e.g.*, $Th(OH)^{+++}$ etc., and in addition thorium hydroxide occurs as positively charged colloidal micelles, the adsorption properties of which are not known. These facts serve to emphasise our previous remarks (Parts I and II) that it is preferable to leave the data in the form of the charge, which can be calculated directly from experimentally measured quantities. Conversion of the charge figures into potentials gives reliable results for uni-univalent electrolytes, but for the higher valencies, the potentials, although of the right order and showing the correct trends with concentration, are probably of rather low accuracy.

Experimental

Materials.—Fused silica powder was cleaned and particle-sized as described in Part I. The water used throughout was equilibrium conductivity water of specific conductivity about 0·8 gemmho. Sodium, barium, and magnesium chlorides were obtained by appropriate recrystallisations of the "AnalaR" salts. Hydrochloric acid was obtained by redistillation of the "AnalaR" acid. Lanthanum chloride was a spectroscopically pure sample supplied in solution by Messrs. Johnson, Matthey and Co., Ltd.; a pure sample of thorium chloride was prepared by Kremer's method (*J. Amer. Chem. Soc.*, 1942, **64**, 1009). All vessels used were treated with alcohol–nitric acid and thoroughly steamed before use.

Sedimentation Experiments.—These were carried out as described previously (Elton, 1949, *loc. cit.*), in a thermostat at 25·00° ± 0·01°. Solutions were prepared by successive dilution, after the suspension had been allowed to settle out. The suspension used throughout, except for the duplicate run with hydrogen chloride solutions, had a surface area per g. (A_0) of $1{\cdot}40_5 \times 10^4$ cm.^{2}, mass per unit volume (M) of $1{\cdot}20_2 \times 10^{-3}$ g./ml., and limiting rate of sedimentation, in concentrated electrolyte solutions (u_0), of $2{\cdot}90_7 \times 10^{-3}$ cm./sec. The suspension used for the duplicate run with hydrogen chloride solutions had $A_0 = 2{\cdot}65_6 \times 10^4$ cm.^{2}, $M = 3{\cdot}14_1 \times 10^{-4}$ g./ml., and $u_0 = 3{\cdot}24_7 \times 10^{-3}$ cm./sec. (Surface areas were determined by the method of catalytic decomposition of hydrogen peroxide, as described in Part I.)

In solutions where the electrokinetic potential was low, the sedimentation meniscus was less sharp than usual, owing to a smaller electroviscous sharpening effect (see Elton, 1951, *loc. cit.*). Also, in such solutions, especially where ζ was less than about 30 mv there was a marked tendency for the particles to undergo some coagulation after the suspension had settled out and stood for a while. When this occurred, the suspension could be returned to its normal state by vigorous mechanical shaking for an hour or more.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, October 17th*, 1952.]

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234. *Quaternary Ammonium Nitrates. Part I. Preparation from Alkyl Nitrates and from αω-Polymethylene Dinitrates.*

By E. S. LANE.

Good yields of quaternary ammonium nitrates are produced by quaternisation of tertiary bases with alkyl nitrates. The reaction has been extended to the production of polymethylenebis(quaternary ammonium nitrates) and of one polymethylenebis(thiuronium nitrate). General features of the reaction are discussed and the pharmacological activity of one compound as a neuromuscular blocking agent is reported.

SINCE the preparation of quaternary ammonium nitrates by metathesis from the corresponding halides is often tedious, it was decided to investigate their formation by direct quaternisation of tertiary bases with alkyl nitrates. Reference has been made to hexamine metho- and etho-nitrates, obtained by reaction of hexamine with the corresponding alkyl nitrate (Hahn and Walter, *Ber.*, 1921, **54**, 153; see also Foss *et al.*, *J.*, 1950, 624), and to the preparation of long-chain quaternary ammonium nitrates by reaction of the higher alkyl nitrates with tertiary bases (B.P. 605,402, Baldwin, Statham, and Imperial Chemical Industries Limited). The latter procedure has now been found to give high yields of the authentic quaternary ammonium nitrates. The reaction has been extended to the production of polymethylenebis(quaternary ammonium nitrates) and of a polymethylenebis (thiuronium nitrate).

Quaternisation of tertiary bases with alkyl nitrates was carried out by refluxing the ester with an excess of tertiary amine, with or without a solvent. Alkyl nitrates are thermally much less stable than the corresponding halides and this leads to some coloration of the quaternised base, but after purification the quaternary ammonium nitrates are obtained (in most cases) as colourless or pale cream-coloured crystals which are soluble in cold water and alcohols but sparingly soluble in cold acetone, ether, and low-boiling light petroleum. The products were characterised by readily crystallised picrates and, in one case, by a crystalline perchlorate. In view of the thermal instability of nitric esters, they were not distilled before quaternisation. Purification of the higher alkyl nitrates was effected by washing them with methanol in which they are only very sparingly soluble. This purification facilitated a high yield of solid higher alkyl quaternary ammonium nitrates.*

Reaction of αω-polymethylene dinitrates with tertiary bases was carried out by the same general procedure. This reaction appears to be general with esters of primary alcohols or glycols, but secondary and tertiary esters show wide differences in behaviour. Simple compounds, *e.g.*, *sec.*-butyl nitrate, reacted normally, but the trinitrate of tristearin-11 : 11′ : 11″-triol (hydrogenated castor oil) yielded no trace of a water-soluble quaternary salt on continued refluxing with several tertiary bases. Similar failure occurred with the nitrate from amyl lactate. With tertiary esters, extensive decomposition occurs, apparently with loss of the elements of nitric acid; for instance, *cyclo*hexyl nitrate reacted with pyridine to yield *cyclo*hexene and polymeric material, whilst 1 : 1 : 3-trimethyltrimethylene dinitrate and pyridine gave an almost quantitative yield of pyridine nitrate together with unidentified polymeric product. *tert.*-Butyl nitrate and pyridine gave a good yield of butylene : no quaternary salt was isolated.

* See also B.P. Appln. 489/1951, assigned to National Research Development Corporation.

The only examples so far encountered of primary nitric ester groups failing to quaternise tertiary bases have been with nitrates of alcohols containing a *neo*pentyl-type of structure, *e.g.*, pentaerythritol, 2 : 2-diethylpropane-1 : 3-diol, and 2-hydroxymethyl-2-methylpropane-1 : 3-diol, where the non-reactivity is almost certainly due to steric hindrance (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 187).

The majority of the nitric esters examined reacted readily with pyridine or trimethylamine, but scarcely at all with higher tertiary amines, *e.g.*, 2-hexylpyridine, tri-*n*-amylamine, even in solvents (*e.g.*, acetonitrile) known to promote quaternisation. Another example of unexplained non-reactivity was observed in the reaction of pentamethylene dinitrate and hexamine, only 5'-nitratopentylhexamine nitrate being obtained.

Pentamethylene dinitrate reacted readily with thiourea, forming pentamethylenebis(thiuronium nitrate) in almost theoretical yield (compare Taylor, *J.*, 1917, **111**, 650).

Polymethylenebis(quaternary ammonium) salts are known to possess considerable neuromuscular blocking activity (Paton and Zaimis, *Brit. J. Pharmacol.*, 1949, **4**, 381; Walker, *J.*, 1950, 193; Taylor, *J.*, 1951, 1150, etc.). Dr. E. J. Zaimis kindly tested some of the compounds described in this paper and reported: " From experiments using the tibialis anterior muscle in the cat, the gastrocnemius muscle in the adult fowl, and the whole chick, it appears that decamethylenebis(pyridinium nitrate) [LD_{50} (intravenously in mice), 7·2 mg. per kg.] is the only one showing an interesting activity at the neuromuscular junction. It possesses considerable anticholinesterase activity (40 times less potent than prostigmine) but at the same time exhibits a direct action causing depolarisation of the motor end plate. To produce a depolarising block comparable with that resulting from decamethonium a dose of about 200 times greater is required. The anticholinesterase activity was tested *in vitro* also. It is proposed to make a more detailed pharmacological study of this compound in the near future."

The pharmacological activity of decamethylenebis(pyridinium bromide) in mice has been reported in less detail by Collier and Taylor (*Nature*, 1949, **164**, 491).

Experimental

Microanalyses are by Drs. Weiler and Strauss, of Oxford.

Cetylpyridinium Nitrate.—Fuming nitric acid (25·4 ml., 0·5 mol.) was added dropwise to acetic anhydride (56·4 ml., 0·5 mol.), cooled and stirred in an ice-bath. The internal temperature being kept at 10°, powdered cetyl alcohol (91 g., 0·375 mol.) was added portionwise (2 hours), and the temperature then allowed to rise to 20°; the mixture was diluted with water (300 ml.), and the aqueous layer removed. The organic layer was purified by shaking it with methanol (3 × 100 ml.), which was only sparingly soluble in the ester. The methanol-washed cetyl nitrate (108 g.) and pyridine (100 ml.) were refluxed for 24 hours, then cooled to 30° and mixed with acetone (to 500 ml. bulk). This solution was cooled in ice, and the precipitated cetylpyridinium nitrate filtered off, recrystallised from acetone (twice), and dried *in vacuo*; the yield of salt, m. p. 62—64°, was 70 g. (Found: C, 68·9; H, 10·4; N, 7·9. Calc. for $C_{21}H_{38}O_3N_2$: C, 68·8; H, 10·4; N, 7·7%). Evers and Klaus (*J. Amer. Chem. Soc.*, 1948, **70**, 3051) give m. p. 58—59°.

Dodecylpyridinium Nitrate.—Dodecyl nitrate (100 g.; from commercial " Lorol ") and pyridine (52 g.) were refluxed for 24 hours, the mixture then being completely water-soluble. Excess of pyridine was removed by steam-distillation, and the still residue diluted with water, boiled with charcoal, and filtered. The colourless filtrate was then evaporated to dryness under reduced pressure. Dodecylpyridinium nitrate was obtained as a straw-coloured wax (98 g.). The *perchlorate* melted at 76·5° (Found: N, 3·75; Cl, 10·2. $C_{17}H_{30}O_4NCl$ requires N, 4·0; Cl, 10·2%).

1-sec.-*Butylpyridinium Nitrate.*—*sec.*-Butyl nitrate (12 g.) and pyridine (20 g.) were refluxed for 8 hours, and the mixture worked up as in the previous example, yielding *sec.*-butylpyridinium nitrate as a water-soluble, golden-yellow, viscous liquid. The corresponding picrate was a yellow oil. Neither compound crystallised.

Preparation of Polymethylene Dinitrates.—Fuming nitric acid (25·4 ml., 0·5 mol.) was added dropwise to acetic anhydride (56·4 ml., 0·5 mol.), cooled and stirred in an ice-bath. The internal temperature being kept below 10°, the polymethylene glycol (0·2 mole) was added portionwise. When the addition was complete the mixture was allowed to warm to room temperature, then

poured into ice–water (500 g.). The oily layer was run off, washed with sodium hydrogen carbonate solution and with water, and dried (Na_2SO_4).

*Preparation of Polymethylenebis(quaternary Ammonium Nitrates).**—The polymethylene dinitrate was refluxed with a two-fold excess of the appropriate tertiary amine. One example is given in detail below; the properties of the quaternary salts are listed in the Table. The reaction involving trimethylamine was carried out in a sealed tube at 100°.

Tetramethylenebis(pyridinium nitrate). Tetramethylene dinitrate (20·7 g.) and pyridine (20 g.) were refluxed for 2 hours. On cooling, the mixture solidified, the solid was filtered off and dissolved in water, and the solution decolorised (charcoal), filtered, and evaporated to dryness (27·4 g.). Recrystallised from methanol, *tetramethylenebis(pyridinium nitrate)* formed pale cream-coloured crystals, m. p. 163—164° (Found: C, 49·6; H, 5·3; N, 16·6. $C_{14}H_{18}O_6N_4$ requires C, 49·7; H, 5·3; N, 16·6%).

Polymethylenebis(quaternary ammonium nitrates and picrates).

	M. p.	Formula	Found: N, %	Req.: N, %
Nitrates				
Tetramethylenebispyridinium		[See above]		
Pentamethylenebispyridinium	106°	$C_{15}H_{20}O_6N_4$	15·7	15·9
Pentamethylenebis-2-hydroxyethyldimethylammonium	123—124	$C_{13}H_{32}O_8N_4$	15·05	15·2
Hexamethylenebispyridinium	194—195	$C_{16}H_{22}O_6N_4$	15·2	15·3
Decamethylenebispyridinium	150—151	$C_{20}H_{30}O_6N_4$	13·1	13·29
Decamethylenebistrimethylammonium	196—198	$C_{16}H_{38}O_6N_4$	13·8	14·0
Decamethylenebisbenzyldimethylammonium	159	$C_{28}H_{46}O_6N_4$	10·6	10·5
Picrates				
Tetramethylenebispyridinium	203 *	—	—	—
Pentamethylenebispyridinium	112—113	$C_{27}H_{24}O_{20}N_{10}$	16·5	16·4
Pentamethylenebis-2-hydroxyethyldimethylammonium	239—240	$C_{25}H_{36}O_{22}N_{10}$	16·1	15·9
Hexamethylenebispyridinium	184—185·5	$C_{28}H_{26}O_{20}N_{10}$	15·8	16·05
Decamethylenebispyridinium	101—102·5	$C_{32}H_{34}O_{20}N_{10}$	14·9	14·9
Decamethylenebistrimethylammonium	146—147 †	—	—	—
Decamethylenebisbenzyldimethylammonium	138·5—139·5	$C_{40}H_{40}O_{20}N_{10}$	12·5	12·9

* Gautier and Renault (*Compt. rend.*, 1947, **225**, 682) give m. p. 207°.
† Zaimis (*Brit. J. Pharmacol*, 1950, **5**, 424) gives m. p. 145—146°.

Polymethylenebis(quaternary ammonium picrates). Analyses are listed in the Table. *Reaction of Pyridine with* 1 : 1 : 3-*Trimethyltrimethylene Dinitrate.*—The dinitrate (20·8 g.), pyridine (16 ml., 2 mol.), and methanol (100 ml.) were refluxed for 8 hours and cooled. The resulting crystalline mass (13 g.) was filtered off, recrystallised from benzene and methanol, and identified as pyridine nitrate, m. p. 114—116° (Found: C, 42·6; H, 4·2; N, 19·1. Calc. for $C_5H_6O_3N_2$: C, 42·3; H, 4·2; N, 19·7%). On evaporation of the filtrate a dark brown, viscous, water-insoluble liquid was obtained which could not be worked up.

Reaction of Pyridine with tert.-*Butyl Nitrate.*—*tert.*-Butyl nitrate (16 g.) and pyridine (16 g.) were refluxed, and the uncondensed vapours from the top of the condenser led into a trap, cooled in solid carbon dioxide. After 1 hour, butylene (6·5 g.; b. p. 1—4°) was recovered from the trap.

Reaction of Pyridine with cyclo*Hexyl Nitrate.*—*cyclo*Hexyl nitrate (15 g.) and pyridine (15 g.) were refluxed for 4 hours. The reaction mixture, which was not water-soluble, was fractionated. The fraction, b. p. 80—84°, was unsaturated, giving an oily dibromide. *cyclo*Hexene boils at 83°.

5′-Nitratopentylhexamine Nitrate.—Pentamethylene dinitrate (5·8 g.) was refluxed for 8 hours with hexamine (9 g.) in ethyl alcohol (50 ml.). The water-soluble reaction mixture was cooled, filtered, and evaporated to dryness, redissolved in water, decolorised (charcoal), filtered, and evaporated *in vacuo*. The pale straw-coloured viscous *nitrate* could not be crystallised (Found: N, 25·2. $C_{11}H_{22}O_6N_6$ requires N, 25·15%). The *picrate* had m. p. 100—102° (Found: N, 21·8. $C_{17}H_{25}O_{10}N_8$ requires 22·4%).

Pentamethylene-1 : 5-*dithiuronium Dinitrate.*—Pentamethylene dinitrate (26 g.), thiourea (21 g., 2 mol.), and "Cellosolve" (150 ml.) were refluxed for 24 hours. Solvent was then removed under reduced pressure, and the residue recrystallised twice from methanol–ether (1 : 1), giving microcrystalline *pentamethylene*-1 : 5-*dithiuronium dinitrate* (12 g.), m. p. 118—119° (Found: N, 23·8; S, 18·4. $C_7H_{18}O_6N_6S_2$ requires N, 24·2; S, 18·5%). The corresponding

* See also B.P. Appln. 13,749/1951, assigned to National Research Development Corporation.

dipicrate melted at 230—231° (Found: N, 21·2; S, 9·5. $C_{19}H_{24}O_{20}N_{12}S_2$ requires N, 20·6; S, 9·4%).

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235. *The Cryoscopic Constants of Dissociating Solvents (with Special Reference to Nitric and Sulphuric Acids).*

By P. A. H. Wyatt.

By making allowance for the heat of dissociation, it is shown that the cryoscopic constants (k_f) of dissociating solvents are expected to vary when the extent of dissociation is altered by added solutes. A method is outlined for investigating simple dissociation equilibria by means of variations in k_f and applied, partially, to Dunning and Nutt's nitric acid data, yielding a heat of dissociation ~10 kcal. Sulphuric acid, a more associated solvent, exhibits a variation of k_f from 5·5 in 0·11M-SO_3 to 6·9 in 0·23M-H_2O, as shown by the use of the non-electrolytes 2 : 4 : 6-trinitrotoluene and nitromethane. This result is not in accordance with the simple treatment and leads to some further discussion on partial molar heat contents in these systems. Empirical k_f values based upon Gillespie, Hughes, and Ingold's data are suggested for the determination of the extent of dissociation of solutes in sulphuric acid.

(1) *General Considerations.*

Although solvents of appreciable dissociation have often been used in cryoscopic investigations, there is one aspect of their theoretical treatment which appears to have escaped attention, namely, that, in cases in which the extent of dissociation can be altered by added solutes, the cryoscopic " constant " will be expected to vary with the extent of such alteration. A familiar example is afforded by the solvent sulphuric acid, in which cryoscopic measurements are usually conducted in the presence of a little water which serves to suppress the dissociation of the solvent. In this case it is not permissible to deduce a cryoscopic constant from thermal data relating to the pure solvent, as Hammett has done (*J. Amer. Chem. Soc.*, 1933, **55**, 1900; 1937, **59**, 1708), or to abstract a single value from experimental data, as Gillespie, Hughes, and Ingold have recently done (*J.*, 1950, 2473—2551), unless it can be shown by special experiments that dissociation heat effects are negligibly small. It is the object of the present paper to draw attention to this point and to attempt some measure of reinterpretation of the data for sulphuric and nitric acids, both of which are believed to have variable cryoscopic constants.

The quantitative argument which follows assumes that changes in the partial molar heat content of the solvent can be explained in terms of species which themselves have constant partial molar heat contents (see, however, Section 3). The heat term, ΔH_f, in the conventional cryoscopic constant, $\boldsymbol{R}T^2/m_1\Delta H_f$, is the heat which is absorbed when 1 mole of the solvent passes from the solid phase into the liquid. If dissociation is suppressed, this heat will simply correspond to the production of undissociated solvent in the liquid phase; but if each mole further dissociates to the fractional extent x, a further amount of heat of magnitude $x\Delta H_d$ will have to be absorbed, ΔH_d being the molar heat of dissociation. (It is assumed that the solid phase is not affected in any way by dissociation changes within the liquid.) The cryoscopic constant (represented hereafter by k_f) therefore becomes $\boldsymbol{R}T^2/m_1(\Delta H'_f + x\Delta H_d)$, where $\Delta H'_f$ represents the heat of fusion of the solvent when its dissociation is completely suppressed, m_1 is the solvent molality, $\boldsymbol{R}$ the

gas constant, and T the hypothetical melting point of the solvent dissociated to the extent x. If x_0 represents the degree of dissociation of the pure solvent, the normal latent heat of fusion can be written as $\Delta H'_f + x_0\Delta H_d$. Now the dissociation of a solvent commonly increases with temperature, so ΔH_d will normally be positive; whence $\boldsymbol{R}T'^2/m_1\Delta H'_f > \boldsymbol{R}T_0^2/m_1(\Delta H'_f + x_0\Delta H_d)$, *i.e.*, k_f will increase with suppression of dissociation. (T' represents the hypothetical melting point of the completely undissociated solvent.)

This formulation shows that the percentage change in k_f could easily be ten times as great as the percentage dissociation; for molar heats of fusion are of the order of 1 kcal., and heats of dissociation of the order of 10 kcal. would not be considered unreasonable (cf. 14 kcal. for water). Thus a pure solvent dissociating only to the extent of 1% could have its cryoscopic constant altered by as much as 10% within the relatively small change of composition required to suppress its dissociation. It also appears that an addition compound AB should have a minimum k_f at the maximum freezing point, and that an increasing excess of either A or B should lead to an increasing k_f, reaching the same maximum on both sides of the composition AB when dissociation has been completely suppressed.

This could be made the basis for an investigation of the dissociation equilibria for such compounds, since the use of a non-electrolyte as an indicator of k_f in solutions of various compositions would give ΔH_d and ΔG_d directly from the same set of cryoscopic data. Even if there is ambiguity about the form of dissociation, such an investigation could help in choosing between alternative forms if used in conjunction with calorimetric data.

(2) *Nitric Acid.*

A complete quantitative analysis in the case of nitric acid is hampered by the fact that there is considerable disagreement between the most recent sets of data for the solutes N_2O_5 and H_2O (Gillespie, Hughes, and Ingold, *J.*, 1950, 2552; Dunning and Nutt, *Trans. Faraday Soc.*, 1951, **47**, 15). Both groups of authors are, however, in agreement in finding larger slopes in the freezing point–molality curves for suppressing solutes than those calculated from Forsythe and Giauque's thermal data (*J. Amer. Chem. Soc.*, 1942, **64**, 48). Gillespie *et al.* have sought to explain this by assuming solvation, using, unfortunately, a formula which is not valid for such high concentrations (especially after allowance for extensive solvation); but a heat of dissociation effect must at once be suspected.

In order to deal with the large concentrations of suppressing solutes and dissociation products involved, it is most convenient in this case to use the mole-fraction type of formula (always assuming of course that Raoult's law is approximated to sufficiently closely), *viz.*:

$$T = T' + (2{\cdot}303\boldsymbol{R}T'^2/\Delta H'_f)(1 - 0{\cdot}00230)\log_{10} N_1$$

Here T is the freezing point of the solution, T' that of the undissociated solvent: 0·00230 contains the usual correction term for variation of ΔH_f with temperature and has been evaluated here with sufficient accuracy from the properties of the pure solvent. The mole-fraction of the solvent is given by the formula

$$N_1 = m_1/(m_1 + \nu_2 m_2)$$

where m_1 and m_2 are the molalities of solvent and solute respectively, and ν_2 represents the number of particles given per solute molecule. [This is not to be confused with the stoicheiometrical mole-fraction, $m_1/(m_1 + m_2)$, used by Dunning and Nutt.]

When Dunning and Nutt's data for ammonium and potassium nitrate were plotted upon this basis (with $\nu_2 = 2$), it was found that they lay upon a common curve, of which the last four points (*i.e.*, for most concentrated solutions) defined a straight line of slope 110 ($= 2{\cdot}303\ \boldsymbol{R}T'^2/\Delta H'_f$), giving $\Delta H'_f = 2250$ cal., and intercept 1·25° above the freezing point of the pure solvent. The abscissa of the point on this straight line at the freezing point of the pure solvent was −0·0113, indicating a mole-fraction of undissociated molecules in the pure solvent of 0·974; and hence $x_0 \sim 0{\cdot}026/\nu_1$ [strictly, this has to be multiplied by $1 + (\nu_1 - 1)x_0$], where ν_1 represents the number of particles given per dissociating solvent molecule. (This method of obtaining x_0 appears to be new. It makes direct use of the condition that the chemical potential of the solvent has the same value in all solutions in

equilibrium with the solid at the same temperature, but requires also the additional assumption that the potential of the undissociated species depends only upon its own mol.-fraction, which will not be valid if interionic attraction effects are important.) If it is now assumed that a simple heat of dissociation effect is being dealt with here, we have for the latent heat of the pure solvent (2503 cal. per mole; Forsythe and Giauque, *loc. cit.*):

$$2503 = \Delta H'_f + x_0\Delta H_d = 2250 + 0{\cdot}026\Delta H_d/\nu_1$$

whence

$$\Delta H_d \sim 10{,}000\nu_1 \text{ cal.}$$

The most popular choice for the main dissociation scheme seems to be $3HNO_3 = NO_2^+ + NO_3^- + H_2O,HNO_3$, having $\nu_1 = 1$; in this case ΔH_d becomes $\sim$10 kcal. Even without the assumption that H_2O is bound to HNO_3 (Chédin, Fénéant, and Vandoni, *Compt. rend.*, 1948, **226**, 1722), the value of ΔH_d is still only 15 kcal.

A value for ΔH_d of this order of magnitude is clearly reasonable enough to suppose that a dissociation heat effect is an important factor here. The thermal changes ascribed to solvation by Gillespie *et al.* (*loc. cit.*, p. 2556) are also consistent with an endothermic solvent dissociation process: thus part of the reason for the greater heat evolved on the addition of water to pure nitric acid than to a solution of dinitrogen pentoxide must be that solvent dissociation is being suppressed in the former case and increased in the latter. Further, Fig. 3 of Dunning and Nutt's paper (*loc. cit.*, p. 21) shows that "cyclonite" gives a greater freezing-point depression in a solution already containing ammonium nitrate than in the pure acid, which is consistent with the present treatment.

More data are required before this view can be accepted with complete confidence, and in view of the uncertainties in the dissociation scheme, and especially in the magnitude of electrostatic forces, the value of 10 kcal. for ΔH_d can at best only be a rough indication.

(3) *Sulphuric Acid.*

The most recent major contribution to the cryoscopic study of sulphuric acid is contained in a series of papers by Gillespie, Hughes, and Ingold and others (*J.*, 1950, 2473—2551), who give full references to earlier work. These authors have introduced considerable improvements in technique and have provided accurate data for a large number of solutes; but the aspect of their work which is of interest at present is that the whole of their interpretation is based upon a single value for k_f of 5·98 deg. mole^{-1} kg. Two features in the choice of this number immediately attract attention in the light of the argument presented here: (i) it is based principally upon the fact that sulphuryl chloride, treated as an ideal non-electrolyte, gives this same value for k_f *whether small amounts of water are present or not*; (ii) it leads to the rejection of the most accurate data available for the latent heat of fusion of pure sulphuric acid. That (i) is an unreliable criterion without special justification is now immediately obvious, since water suppresses the dissociation of sulphuric acid; and the rejection of accurate calorimetric latent heats shows that there is at least a case for enquiry here.

Further, Gillespie concludes (*loc. cit.*, p. 2547) that nitromethane undergoes ionization on the basis of its behaviour in a solution containing 0·060M-water (Expt. 33), where it gives a molar depression of 6·57. Yet the molar depression found in Expt. 32 (of which, however, full details are not given—see p. 2482) is 6·25, which is not consistent with the same degree of ionization; and, since the molality of water in the second experiment was 0·04, a variation in k_f with the amount of water added is at once suspected. In support of this conclusion, it is observed that 2 : 4 : 6-trinitrotoluene, which had hitherto always been regarded as a non-electrolyte in these systems, gives a molar depression of 6·65 in a solution containing 0·074M-water (p. 2544). Accordingly, an investigation was undertaken in which these two solutes were regarded as ideal non-electrolytes which would serve as indicators of k_f at various compositions. During the course of this work, valuable corroboration has appeared from Brand, Horning, and Thornley (*J.*, 1952, 1374), who have shown by spectrophotometric methods that 2 : 4 : 6-trinitrotoluene is in fact a non-electrolyte in 100% H_2SO_4. These authors noticed the discrepancy between this and the cryoscopic ν-value but suggested tentatively a solvation hypothesis.

Freezing Points of Nitromethane and TNT *Solutions.*—The molar depressions of the freezing point of sulphuric acid produced by the two solutes nitromethane and 2 : 4 : 6-trinitrotoluene have been determined at compositions round about the maximum. The method used was the same as that of Gillespie, Hughes, and Ingold except that a Beckmann thermometer and a mechanical stirrer protected by a mercury-trap were used in place of the more satisfactory devices of these authors. The same super-cooling correction was also applied, although their factor, 0·012, will obviously need reconsideration.

In Tables 1 and 2, m_2 represents the solute molality, θ the depression of the freezing point from that of the solvent containing the amount of SO_3 or H_2O specified; and k_f values (in deg. mole^{-1} kg.) are calculated simply as θ/m_2. In making these

TABLE 1.

2 : 4 : 6-Trinitrotoluene as solute.

$SO_3 = 0{\cdot}113m$			$SO_3 = 0{\cdot}005m$			$H_2O = 0{\cdot}23m$		
m_2	θ	k_f	m_2	θ	k_f	m_2	θ	k_f
0·0325	0·176	5·4	0·0210	0·124	5·9	0·0190	0·134	7·1
0·0941	0·519	5·5	0·0327	0·191	5·8	0·0413	0·280	6·8
		5·5	0·0544	0·322	5·9	0·0757	0·526	6·9
			0·0812	0·481	5·9	0·0940	0·644	6·9
					5·9			6·9

TABLE 2.

Nitromethane as solute.

$SO_3 = 0{\cdot}054m$		
m_2	θ	k_f
0·0351	0·189	5·4
0·0881	0·481	5·5
0·1524	0·889	5·8
0·1954	1·115	5·7
0·2400	1·388	5·8
		5·6

measurements, it was found that, even when conditions were kept constant during crystallization, it was still possible to produce capricious errors, particularly on the SO_3 side of the maximum, where amongst a series of readings agreeing to 0·005° an occasional difference of as much as 0·02° was recorded. Such random values were ignored and, in any case, cannot affect the general character of the results quoted above (especially for the higher molalities); but in view of them k_f values are only recorded to one place of decimals and minor corrections (for variation of ΔH_f with temperature and the effect on the solvent mole-fraction of the third component, *i.e.*, SO_3 or H_2O) were not applied.

TABLE 3. *Summary of* k_f *values.*

$[SO_3]$, m	k_f	$\bar{L}$ for H_2SO_4 relative to pure H_2SO_4 (calc.)	$[H_2O]$, m	k	$\bar{L}$ for H_2SO_4 relative to pure H_2SO_4 (calc.)
0·113	5·5	300	0·04 *	6·25	−40
0·054	5·6	250	0·06 *	6·57	−160
0·005	5·9	110	0·074 *	6·65	−190
			0·23	6·9	−280

* Gillespie, Hughes, and Ingold's data (*loc. cit.*).

Conclusions concerning Sulphuric Acid.—Table 3 shows that if these nitro-compounds can be regarded as ideal non-electrolytes, the cryoscopic constant must vary continuously through the range of SO_3–H_2O composition studied. Thus in looking for the type of variation described in Section (1), one of a different type has been found, for there is no sign of the minimum expected from the simple treatment. One feature of importance is, however, that there is no reason to doubt that k_f will lie at about 6·1 in the composition of maximum freezing point, as required by the latent heat of fusion (Brønsted, 2550 cal.; Rubin, 2561 cal.; giving k_f 6·15 and 6·12 respectively).

Table 3 also contains the values calculable from k_f (*via* ΔH_f) of the partial molar heat content of sulphuric acid relative to the pure solvent. Kunzler and Giauque (*J. Amer. Chem. Soc.*, 1952, **74**, 3472) have already pointed out that all the former heat-content data, including those of Brønsted, are unreliable in this region of composition: although Brønsted's data (*Z. physikal. Chem.*, 1909, **68**, 693) show a variation of only 170 cal. in $\bar{L}_1$ for water from 0·0M to 0·5M, yet these authors quote an 8000 cal. change in $\bar{L}_1$ for a change of only 0·07M-water near 100% H_2SO_4. When the data of Table 3 for the solvent are plotted on a graph, they define an S-shaped curve bearing a striking resemblance to Kunzler and Giauque's Fig. 2 (*loc. cit.*, p. 3475), but with the curvature in the opposite

direction, as required theoretically. Giauque has not yet published his calculations for $\bar{L}_2$, but it must be admitted that his variations in $\bar{L}_1$ would lead to smaller changes in $\bar{L}_2$ than those recorded in Table 3. On the other hand, the calorimetric determination of these quantities in this region involves experimental difficulties and Kunzler and Giauque actually mention a source of error (*loc. cit.*, p. 3475). It is also possible that the temperature difference may play a part; for the highly associated, or quasi-crystalline, structure near the freezing point (cf. Ubbelohde, *Quart. Reviews*, 1950, **4**, 361) would be somewhat broken down 15° higher. (This would be reflected in a highly detailed C_p curve; cf. Kunzler and Giauque, *loc. cit.*, p. 3476.) The detailed shape of the solvent $\bar{L}$ curve in the immediate neighbourhood of 100% H_2SO_4 is a matter of considerable importance; for if there were not an additional curvature in this region making $\partial\bar{L}/\partial N_s = 0$ when N_s is zero (where N_s refers to the solute mole-fraction), $\bar{L}$ for the solute would be infinite at that point, and this is not possible since μ (the chemical potential) and $(\partial\mu/\partial T)_p$ are both finite for a dissociation product when $N_s = 0$. There is some indication (on the water side) of such a second curvature, but more extensive data are required before this test can be applied with confidence.

It seems likely that accurate k_f or direct ΔH_f measurements may provide the best means of determining $\bar{L}$ in this region, in which connection it may be significant that Table 3 would demand considerably less water contamination during the ΔH_f determinations by Brønsted's precursors than he himself calculated (*loc. cit.*, p. 712). The highly associated structure of sulphuric acid provides a possible explanation for such large heat changes, the $\bar{L}$ data being in the direction expected for structure-breaking by SO_3 and structure-building by H_2O. The low k_f values recorded for sulphuryl chloride and chlorosulphonic acid by Gillespie, Hughes, and Ingold (*loc. cit.*, p. 2481) might also be due to structure-breaking, as their structural similarity to SO_3 suggests. [Ramsay (*J.*, 1894, **65**, 167; *Z. physikal. Chem.*, 1893, **12**, 433) ascribed to H_2SO_4 an association factor of 32, as against 3·8 for H_2O and 1·7 for HNO_3—at room temperature, however.] But further investigations of $\bar{L}$ and k_f changes for other compounds are required before it can be decided how unusual H_2SO_4 is in this respect, and whether the effect found is merely masking or actually displacing variations of the type described in Section (1) (expected from $x_0 \sim 0{\cdot}002$ to be of the order of a few units % in this case).

The behaviour of the nitro-compounds is not the only evidence for a variable k_f. Despite the interionic-attraction effects expected (Brand, Horning, and Thornley, *loc. cit.*), potassium and ammonium sulphates in the anhydrous acid still give greater molar depressions than would be expected from $k_f = 6{\cdot}1$ after suppression of solvent dissociation (Gillespie *et al.*, *loc. cit.*, pp. 2487, 2488). The actual values of T' and k'_f obtained graphically as for nitric acid in Section (2) (the formula of Gillespie *et al.*, p. 2478, being used without assumptions as to solvation) were

$$K_2SO_4: \; T' = 10{\cdot}62°, \; k'_f = 6{\cdot}48$$
$$(NH_4)_2SO_4: \; T' = 10{\cdot}54°, \; k'_f = 6{\cdot}17$$

It is true that Gillespie *et al.* have used the same data to support $k_f = 5{\cdot}98$, but there are two arguments against this: (*a*) they assumed solvation sufficient to give a constancy in k_f which was far better than anything achieved with sulphuryl chloride; (*b*) they used a fixed value of 10·52° for T' in assessing constancy in the derived k_f values, which is tantamount to investigating the slope of a graph whilst keeping the intercept on the *y* axis rigidly fixed. This uncertainty in T' weakens the argument advanced by these authors in support of their two forms of dissociation $2H_2SO_4 = H_3SO_4^+ + HSO_4^-$ and $2H_2SO_4 = H_3O^+ + HS_2O_7^-$; for upon the basis of the difference in their values of T' for inorganic sulphates (10·52°) and water (10·62°) they conclude that only the first of these dissociations is suppressed by the addition of bisulphates since the second does not yield HSO_4^-. It is noteworthy that this argument is unsound in any case, as consideration of the connecting equilibrium $H_2SO_4 = H_2O + SO_3$ (or any of its alternative forms, *e.g.*, $2H_2SO_4 = H_3O^+ + HSO_4^- + SO_3$) will show; for any increase in the potential of the water brought about by adding either of its dissociation products must be accompanied by a decrease in

the potential of SO_3 ($= \mu_{H_2SO_4^+} + \mu_{HS_2O_7^-}$ in their scheme): *i.e.*, all forms of dissociation must be suppressed by any of the dissociation products.

This removes an objection to the form of dissociation suggested (for H_2SO_4 as a solute, however) by Stubbs, Williams, and Hinshelwood (*J.*, 1948, 1065), *viz.*, $3H_2SO_4 = HSO_3^+ + H_3O^+ + 2HSO_4^-$, which contains the ionization of SO_3 into HSO_3^+ and HSO_4^-. This form of dissociation would provide a step towards the unification of the theory of oleum solutions, for Brand has already assumed the presence of HSO_3^+ in kinetic studies (*J.*, 1950, 1004); it is also obviously analogous to the NO_2^+ dissociation of nitric acid.

Amongst other conclusions from cryoscopic work which now require reconsideration are: the applicability of Raoult's law (in view of the $\bar{L}$ changes), the elimination of interionic-attraction effects by an extremely high dielectric constant, and the incompleteness of the ionization of water.

The Determination of ν*-Values for Solutes.*—When water and hydrogen sulphates are present together as solutes, the disentangling of activity and thermal effects is complicated. The principal use of cryoscopic measurements in sulphuric acid, however, has been in the determination of ν-values (as defined by Gillespie, Hughes, and Ingold), and in this respect the linear relation between molality and freezing point, observed for many compounds in solutions containing a little water, may be utilized in an empirical way despite the probability of its being the fortunate resultant of a number of opposing effects. From the practical point of view, therefore, it is suggested that the following k_f values should be used in this application: they have been derived from a survey of Gillespie's results:

For $\nu \geqslant 2$, $k_f = 6{\cdot}0$, unless water is suspected as a dissociation product, in which case $k_f = 5{\cdot}9$.

For $2 \geqslant \nu \geqslant 1$, $k_f \sim 6{\cdot}6 - (\nu - 1)0{\cdot}6$ (for $m_{H_2O} \sim 0{\cdot}06$, for example). It is stressed that these values are purely empirical and that they should be applied directly to the data, *without any corrections whatsoever* (apart from the practical estimate of the supercooling error): *i.e.*, $\nu = \theta_{obs.}/k_f m_2$, where $\theta_{obs.}$ is the observed depression from the freezing point of the solvent treated with water. Deviations of 1 or 2% from whole numbers cannot be given any significance since unknown heat effects may be introduced with every new system.

The foregoing discussion shows that in the long controversy over the value of k_f, in which various values ranging from 6 to 7 have been defended, all the authors could have been right for their particular conditions, but were mistaken in regarding it as a constant quantity.

This approach may also have relevance in the study of molten electrolytes, where discrepancies between calorimetric and cryoscopic latent heats are not uncommon.

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236. *The Thermochemistry of Organo-arsenic Compounds. Part II.* Esters of Arsenious Acid.*

By T. Charnley, C. T. Mortimer, and H. A. Skinner.

Values are reported for the heats of hydrolysis in 4N-sodium hydroxide at 25° of trimethyl, triethyl, and tripropyl arsenite. The heats of formation of the esters have been derived as follows (in kcal./mole):

$\Delta H_f°$ [$As(OMe)_3$, liq.] = − 141·3 ± 0·7; $\Delta H_f°$[$As(OEt)_3$, liq.] = − 168·8 ± 0·7;
$\Delta H_f°$ [$As(OPr)_3$, liq.] = − 190·0 ± 1·6.

From measurements of the vapour pressures over a range of temperature, latent heats of vaporization were obtained:

$\Delta H_{vap.}(Me_3AsO_3)$ = 10·06 ± 0·14, $\Delta H_{vap.}$ (Et_3AsO_3) = 11·76 ± 0·46 kcal./mole.

The thermal data are used to derive values of the *mean* bond dissociation energies, $\overline{D}$(As–OR), in the alkyl arsenites. The variations in these $\overline{D}$ values are discussed.

The lower members of the series of esters of arsenious acid, $As(OR)_3$, are rapidly and completely hydrolysed by water to give the alcohols, ROH, and precipitated arsenious oxide. For the purpose of thermochemical study, hydrolysis in the presence of excess of alkali, yielding products *in solution*, is preferable to aqueous hydrolysis, and was the method adopted in the present work.

The heats of hydrolysis provide values for the heats of formation of the esters, $\Delta H_f°$[$As(OR)_3$], in terms of the heat of formation of arsenious oxide. The latter is reasonably well established, and we have accepted the value, $\Delta H_f°(As_2O_3$, cryst., octahedral) = −156·97 kcal./mole, recommended in the "Tables of Selected Values of Chemical Thermodynamic Properties" (Nat. Bur. Standards, Washington, Circular 500, 1952).

The thermochemical results can be translated into values for the *mean* bond dissociation energies, $\overline{D}$(As–OR), in this series of esters, by use of a procedure similar to that of Charnley, Skinner, and Smith (*J.*, 1952, 2288) in a comparable study on the esters of boric acid.

Experimental

Preparation of Compounds.—The arsenious esters were prepared by Crafts's method (*Bull. Soc. chim.*, 1870, **14**, 102), *viz.*, reaction of the appropriate sodium alkoxide with excess of arsenic trichloride. Unchanged arsenic trichloride was removed by precipitation with gaseous ammonia. The crude esters were purified by fractional distillation under reduced pressure through a 6″ column packed with stainless steel gauze, designed by Imperial Chemical Industries Limited, Billingham. Samples were retained boiling over the ranges given below: $As(OMe)_3$ 27·2—27·4°/10 mm.; $As(OEt)_3$ 46·3—46·6°/6 mm.; $As(OPr)_3$ 81·3—81·6°/5·5 mm. These were further distilled in a high vacuum, and the pure products collected and sealed in thin, weighed, glass ampoules.

Calorimeter.—The calorimeter was identical with that described in Part I (*loc. cit.*). The experiments were conducted by breaking the ampoules containing known amounts of ester under the surface of 750 c.c. of 4N-sodium hydroxide in the Dewar vessel. As a precaution against atmospheric oxidation of the products, a slow stream of moist nitrogen was passed over the surface of the solution throughout the experiments. Temperature changes were measured in terms of the resistance changes in a shielded thermistor element immersed in the reaction solution. The calorimeter was calibrated electrically, by the substitution method.

Units.—All heat quantities are given in units of the thermochemical calorie, defined as: 1 calorie = 4·1840 abs. joules. The reactions were performed at 25°.

Results.—Preliminary experiments, in which ampoules of trimethyl arsenite were broken under water, showed that the hydrolysis occurs extremely rapidly, but that subsequent dissolution of the resulting arsenious oxide is slow. This feature renders the purely aqueous hydrolysis less satisfactory for thermal study than the hydrolysis by aqueous alkali, in which arsenious oxide dissolves comparatively speedily. Schulman and Schumb (*J. Amer. Chem. Soc.*,

* Part I, *J.*, 1952 4331.

1943, **65**, 879) reported values for the heats of solution of the two crystalline forms of arsenious oxide in 4N-sodium hydroxide, and this fact decided our choice of medium for the hydrolysis reactions.

The observed heats of reaction in 4N-sodium hydroxide are given under $\Delta H_{obs.}$ in Table 1. These values refer to the overall reactions :

$$2As(OR)_3 \text{ (liq.)} + 3H_2O, \text{ in excess of 4N-NaOH} \longrightarrow (6ROH + As_2O_3), \text{ dissolved in 4N-NaOH} \quad (1)$$

The values given under $\Delta H_{hyd.}$ are the heats of the ideal hydrolysis reactions :

$$2As(OR)_3 \text{ (liq.)} + 3H_2O \text{ (liq.)} \longrightarrow 6ROH \text{ (liq.)} + As_2O_3 \text{ (octahedral)} \quad . \quad . \quad . \quad (2)$$

The relation between $\Delta H_{obs.}$ and $\Delta H_{hyd.}$ is expressed by

$$\Delta H_{hyd.} = \Delta H_{obs.} - \Delta H_{soln.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $\Delta H_{soln.}$ = heat of solution of the products of reaction (2) in excess of 4N-sodium hydroxide.

The terms contributing to $\Delta H_{soln.}$ include (*a*) the heat of solution of crystalline (octahedral) arsenious oxide in 4N-sodium hydroxide, for which Schulman and Schumb (*loc. cit.*) quote $\Delta H = -13{\cdot}42 \pm 0{\cdot}1$ kcal./mole of As_2O_3, and (*b*) the heats of solution of the alcohols (ROH

TABLE 1. *Heats of hydrolysis of alkyl arsenites.*

R_3AsO_3 (g.)	$-\Delta H_{obs.}$ (kcal.)	$-\Delta H_{hyd.}$ (kcal.)	R_3AsO_3 (g.)	$-\Delta H_{obs.}$ (kcal.)	$-\Delta H_{hyd.}$ (kcal.)	R_3AsO_3 (g.)	$-\Delta H_{obs.}$ (kcal.)	$-\Delta H_{hyd.}$ (kcal.)
Methyl arsenite			Ethyl arsenite			Propyl arsenite		
4·6838	36·7	12·2	3·1286	35·4	12·5	5·6951	31·5	11·3
4·2266	35·7	11·2	2·5846	35·7	12·8	5·2899	31·6	11·4
4·3435	36·0	11·5	4·4918	35·5	12·6	4·7982	32·3	12·1
4·3507	35·8	11·3	3·8344	35·6	12·7	3·8306	31·7	11·5
4·0938	36·6	12·1	3·5562	35·7	12·8	6·5557	32·5	12·3
4·4704	36·1	11·6						
3·8930	36·3	11·8		Mean	$-12{\cdot}7 \pm 0{\cdot}3$		Mean	$-11{\cdot}7 \pm 1{\cdot}2$
	Mean	$-11{\cdot}7 \pm 0{\cdot}6$						

liq.) in 4N-sodium hydroxide. These were measured for each of the three alcohols concerned, under conditions adjusted to match those in the corresponding ester hydrolyses. The following values (in kcal./mole of ROH) were obtained : MeOH(liq.) = $-1{\cdot}85 \pm 0{\cdot}01$; EtOH(liq.) = $-1{\cdot}58 \pm 0{\cdot}01$; PrOH(liq.) = $-1{\cdot}13 \pm 0{\cdot}10$: these values differ appreciably from those obtained for solution in pure water (Charnley, Skinner, and Smith, *loc. cit.*).

The values of $\Delta H_{soln.}$ appropriate to equation (3) are thus : $-24{\cdot}52 \pm 0{\cdot}16$, $-22{\cdot}90 \pm 0{\cdot}16$, and $-20{\cdot}20 \pm 0{\cdot}7$ kcal./mole for R = Me, Et, and Pr, respectively.

TABLE 2. *Heats of formation of alkyl arsenites,* R_3AsO_3.

R	$\Delta H_f°$ (liq.) * (kcal./mole)	$\Delta H_f°$ (gas) (kcal./mole)	R	$\Delta H_f°$ (liq.) * (kcal./mole)	$\Delta H_f°$ (gas) (kcal./mole)	R	$\Delta H_f°$ (liq.) * (kcal./mole)	$\Delta H_f°$ (gas) (kcal./mole)
Me	$-141{\cdot}3 \pm 0{\cdot}7$	$-131{\cdot}2 \pm 0{\cdot}9$	Et	$-168{\cdot}8 \pm 0{\cdot}7$	$-157{\cdot}0 \pm 1{\cdot}2$	Pr	$-190{\cdot}0 \pm 1{\cdot}6$	$-177{\cdot}4 \pm 2{\cdot}1$

* The errors quoted are the overall errors, obtained by *addition* of the experimental errors in our measurements, and errors present in assumed thermal data.

Table 2 gives the heats of formation of the alkyl arsenites, derived from the equation :

$$\Delta H_f° [As(OR)_3, \text{ liq.}] = 3\Delta H_f° (ROH, \text{ liq.}) + \tfrac{1}{2}\Delta H° (As_2O_3, \text{ c., octa.}) - \tfrac{3}{2}\Delta H_f° (H_2O, \text{ liq.}) - \tfrac{1}{2}\Delta H_{hyd.} \quad (4)$$

which is the thermal description of the ideal hydrolysis reaction in equation (2). The values adopted for the standard heats of formation on the right-hand side of equation (4) were, in kcal./mole, as follows : MeOH(liq.) = $-57{\cdot}04 \pm 0{\cdot}05$, EtOH(liq.) = $-66{\cdot}39 \pm 0{\cdot}10$, PrOH(liq.) = $-73{\cdot}27 \pm 0{\cdot}25$, H_2O(liq.) = $-68{\cdot}32 \pm 0{\cdot}01$, and As_2O_3 (c., octa.) = $-156{\cdot}97 \pm 0{\cdot}5$.

The $\Delta H_f°$ [$As(OR)_3$, gas] values, also given in Table 2, are related to the $\Delta H_f°$ obtained from equation (4) through :

$$\Delta H_f° [As(OR)_3, \text{ gas}] = \Delta H_f° [As(OR)_3, \text{ liq.}] + \Delta H_{vap.} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $\Delta H_{vap.}$ is the heat of vaporisation of $As(OR)_3$. The latent heats of vaporisation of the methyl and ethyl esters were obtained from a series of measurements over a range of temperature of the vapour pressures of the two compounds, in an apparatus similar to that described by Schlesinger and Burg (*J. Amer. Chem. Soc.*, 1937, **59**, 780). The results obtained are summarized in Table 3; values of $\Delta H_{vap.}$ were calculated from the Clausius–Clapeyron equation.

TABLE 3. *Vapour pressure, p,* of methyl and ethyl arsenite.*

Temp. (° c)	Me_3AsO_3, *p*	Et_3AsO_3, *p*	Temp. (° c)	Me_3AsO_3, *p*	Et_3AsO_3, *p*	Temp. (° c)	Me_3AsO_3, *p*	Et_3AsO_3, *p*
27·0°	10·7	—	42·0°	24·0	4·83	57·0°	49·5	11·12
32·0	14·0	2·46	47·0	30·9	6·48	62·0	62·1	14·59
37·0	18·5	3·47	52·0	39·2	8·53	67·0	—	18·58

* Values of *p* in mm. of Hg of *d* 13·60. The average error in the pressure readings is *ca.* 1% for $As(OMe)_3$, and 4% for $As(OEt)_3$.

The vapour pressures in Table 3 may be expressed by $\log_{10} p = -m/T + c$ (with T in °K), and where $m = 2200$, $c = 8{\cdot}358 \pm 0{\cdot}003$ for $As(OMe)_3$, and $m = 2570$, $c = 8{\cdot}831 \pm 0{\cdot}008$ for $As(OEt)_3$. The calculated values of $\Delta H_{vap.}$ are respectively $10{\cdot}06 \pm 0{\cdot}14$ and $11{\cdot}76 \pm 0{\cdot}46$ kcal./mole, respectively. The value of $\Delta H_{vap.}$ for $As(OPr)_3$ ($12{\cdot}6 \pm 0{\cdot}5$ kcal./mole) was obtained by combining our observed b. p. (at 5·5 mm.) with others from the literature, and constructing from these the pressure–temperature equation for this compound.

DISCUSSION

We define the *mean* bond dissociation energy, $\bar{D}$(As–OR), in an alkyl arsenite $As(OR)_3$, as one-third of the heat of the dissociation process :

$$As(OR)_3\ (g.) \longrightarrow As\ (g.) + 3\ {\cdot}OR\ (g.) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The defining thermochemical equation is thus

$$\bar{D}(As{-}OR) = \tfrac{1}{3}\Delta H_f^\circ\ (As,\ g.) + \Delta H_f^\circ\ ({\cdot}OR,\ g.) - \tfrac{1}{3}\Delta H_f^\circ\ [As(OR)_3,\ g.] \quad . \quad . \quad . \quad . \quad (7)$$

Of the terms in equation (7), those in ΔH_f° [$As(OR)_3$, g.] are given in Table 2, and the value ΔH_f° (As, g.) = 60·64 kcal./mole is recommended in the National Bureau of Standards tables (*loc. cit.*). The terms in ΔH_f° (·OR, g.) present some difficulty, for only in one case (·OR = ·OEt) is the value satisfactorily established. Rebbert and Laidler recently (*J. Chem. Physics*, 1952, **20**, 574) obtained ΔH_f° (·OEt, g.) = −8·1 ± 1 kcal./mole, from a study of the kinetics of thermal decomposition of diethyl peroxide.

Charnley, Skinner, and Smith (*loc. cit.*), following a suggestion by Gray (*Discuss. Faraday Soc.*, 1951, **10**, 310), derived ΔH_f° (·OEt, g.) = −8·7 kcal./mole, by equating the activation energy of the unimolecular decomposition of ethyl nitrite (Steacie and Shaw, *J. Chem. Physics*, 1934, **2**, 345) to the heat of rupture of the O–N bond. This estimate is in good agreement with Rebbert and Laidler's value, and lends support to the estimate of ΔH_f° (·OMe, g.) = −1·9 kcal./mole, obtained from a similar argument applied to methyl nitrite. For our present purpose, we adopt the value ΔH_f° (·OMe, g.) = −1·3 kcal./mole; this preserves the *difference* (−6·8 kcal.) between the heats of formation of ·OMe and ·OEt given by Charnley *et al.*, whilst alteration is made to adjust ΔH_f° (·OEt, g.) to Rebbert and Laidler's value. Lack of suitable experimental data prevents an estimate by similar methods of ΔH_f° (·OPr, g.), and for this quantity we adopt a provisional value, ΔH_f° (·OPr, g.) = −13 kcal./mole, obtained by consideration of the probable trend in D(RO–H) in the series of aliphatic alcohols. With these values of ΔH_f° (·OR, g.), equation (7) leads to the values of $\bar{D}$(As–OR) listed in Table 4. For comparison, values of

TABLE 4. *Mean bond-energy values.*

·OR	ΔH_f° (·OR, g.), (kcal./mole)	$\bar{D}$(As–OR), (kcal.)	$\bar{D}$(B–OR), (kcal.)	D(H–OR) (kcal.)
·OMe	−1·3 ± 2	62·64 ± 2·3	103·0 ± 2·3	98·9
·OEt	−8·1 ± 1	64·45 ± 1·4	104·67 ± 1·4	100·3
·OPr	−13 ± 2	66·44 ± 2·7	106·37 ± 2·8	101·3

$\bar{D}$(B–OR) in the alkyl borates (Charnley, Skinner, and Smith, *loc. cit.*), and of D(H–OR) in the alcohols are also given.

It is noteworthy that the D(As–OR) values are smaller than the *mean* bond dissociation of the As–O bonds in gaseous As_4O_6, for which the value D(As–O) = 73·3 kcal./mole has been derived (Part I, *loc. cit.*). One possible cause of this may lie in the resonance (" hyperconjugation ") stabilization of the radicals ·OR (cf. Roberts and Skinner, *Trans. Faraday Soc.*, 1949, **45**, 339).

To illustrate this, we may consider the values of $\overline{D}$(Me–O) and D(Me–OMe) in dimethyl ether. One may derive from existing thermal data [$\Delta H_f°$ (Me_2O, g.) = −44·3 kcal./mole (N.B.S. Tables, *loc. cit.*); $\Delta H_f°$ (Me, g.) = 32·6 ± 1 kcal./mole (Mortimer, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220)]

(1) Me_2O (g.) ⟶ 2Me (g.) + O (g.); ΔH_1 = 168·6 kcal.

(2) Me_2O (g.) ⟶ Me (g.) + ·OMe (g.); ΔH_2 = 75·6 kcal.

whence $\overline{D}$(Me–O) = $\frac{1}{2}\Delta H_1$ = 84·3 kcal., and D(Me–OMe) = ΔH_2 = 75·6 kcal. mole. The difference between these values (8·7 kcal.) is comparable with that between $\overline{D}$(As–O) and $\overline{D}$(As–OMe), and arises, we suggest, from resonance stabilization in the methoxy-radical. There is reason to believe that there is an appreciable resonance stabilization in the *ethyl* radical, arising from π-hyperconjugation (cf. Wheland, *J. Chem. Physics*, 1934, **2**, 474; Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41), and one might expect a similar effect in the *methoxy*-radical, particularly if the oxygen atom adopts a trigonal, or near-trigonal disposition of its bonded electron pair with respect to its two lone-pairs of non-bonding electrons, leaving the odd electron free to conjugate, as a π-electron, with the $-C{\equiv}H_3$ group.

The variations in $\overline{D}$(As–OR) with changing R are matched by parallel variations in the values D(H–OR). Empirical evidence suggests that the latter increase as R ascends the series R = Me, Et, Pr, Bu^t [Murawski, Roberts, and Szwarc, *J. Chem. Physics*, 1951, **19**, 698, give D(H–O–Bu^t) = 106 kcal./mole], implying decreasing resonance stabilization (π-hyperconjugation) in the radicals ·OR of this series. Alternatively expressed, it seems that π-hyperconjugation is strongest in ·O–CH_3, and decreases with methyl (or alkyl) substitution in the methoxy-group.

THE UNIVERSITY, MANCHESTER, 13. [*Received, November 27th*, 1952.]

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237. 2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphoxide and* 2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphone.*

By HELENA BRADBURY, F. J. SMITH, and F. A. TALMAN.

The substance, m. p. 241°, obtained by oxidation of 2 : 2′ : 4 : 4′-tetranitrodiphenyl sulphide is stated in the literature to be the corresponding sulphone. It is now shown to be the sulphoxide. The corresponding sulphone, m. p. 175°, has been prepared, both by direct oxidation of the sulphide and by further oxidation of the sulphoxide.

IT is well known that diaryl sulphides may be oxidised successively to the corresponding sulphoxides and sulphones, by, *e.g.*, hydrogen peroxide or chromium trioxide in acetic acid or by fuming nitric acid. The ease of oxidation depends on the number and nature of the substituent groups in the aromatic nuclei, and Blanksma (*Rec. Trav. chim.*, 1901, **20**, 425) reports that dipicryl sulphide resists nitric acid (*d* 1·52) at 200°.

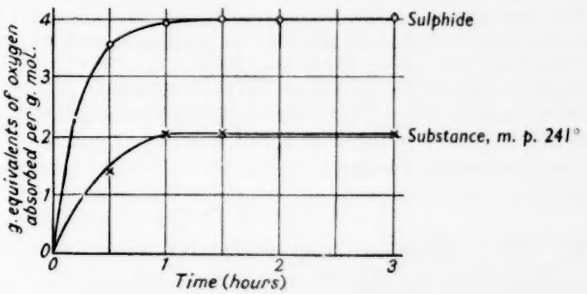
Beilstein and Kurbatow (*Annalen*, 1879, **197**, 75) heated 2 : 2′ : 4 : 4′-tetranitrodiphenyl sulphide for 6 hours with nitric acid (*d* 1·52) in a sealed tube at low pressure and isolated a pale yellow product, m. p. 241°. This they concluded was the sulphone, undeterred by a discrepancy of 10% in the sulphur analysis. Blanksma (*loc. cit.*) obtained the "sulphone," m. p. 240°, from the sulphide by using chromium trioxide in acetic acid; the analysis does not support his conclusion that this substance is the sulphone, for by arithmetical error the calculated percentage of sulphur is given as 8·25% instead of 8·04%; he found 8·28%, which agrees much more closely with the value for the sulphoxide.

From the behaviour of dipicryl sulphide cited above, it appeared to us that the product of m. p. 241° could be the sulphoxide. When the sulphide was refluxed with a very large excess of chromium trioxide in glacial acetic acid for at least 6 hours, an almost white neutral substance of m. p. 175° was obtained in good yield. This resists further oxidation even by potassium dichromate in concentrated sulphuric acid, and may be conveniently

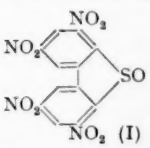
and rapidly prepared directly from the sulphide by means of this reagent. Oxidation of the product, m. p. 241°, by either of these methods also yields that of m. p. 175°.

Sulphur analyses indicate that the products of m. p. 241° and 175° are respectively the sulphoxide and sulphone, and this is supported by the following quantitative oxidations.

A 1% solution of potassium dichromate in 80 : 100 (v/v) sulphuric acid–water can be boiled for a long period with negligible loss of oxidising power and the rate of attack by the boiling reagent on the sulphone is extremely slow. This afforded a basis for quantitative oxidation of the sulphide and the product, m. p. 241°; control blanks contained the same volume of oxidising solution, together with an amount of product, m. p. 175°, equal to that which would finally be formed by oxidation. The results are shown in the Figure, those for the product of m. p. 241° being based on its being the sulphoxide. For all points lying on the horizontal parts of the curves, the final product had m. p. 175°. Our contention is thus proved, except for a slight possibility that the final product might be a cyclised sulphoxide (I).



Attempts to synthesise the sulphone by an unequivocal method proved unsuccessful, but the material of m. p. 175° underwent " sulphone exchange " (Louden, *J.*, 1935, 537) with sodium toluene-*p*-sulphinate, yielding 2 : 4-dinitrophenyl *p*-tolyl sulphone. This alone does not prove that the substance is a sulphone, since an identical product is obtained, though with greater difficulty, from sodium toluene-*p*-sulphinate and the product of m. p. 241°, which suggests nucleophilic attack by the sulphinate ion on the $C_{(1)}$ in both cases, the sulphonyl group in the resultant unsymmetrical sulphone originating from the attacking sulphinate ion. It does, however, exclude the cyclised sulphoxide structure (I).



(I)

Our identification of the product, m. p. 241°, is at variance with the results of Hodgson and Dodgson (*J.*, 1948, 1002) who claim to have prepared the sulphoxide, m. p. 190°, by the action of nitric acid (*d* 1·52) on the sulphide at room temperature for an hour. We find that this method invariably yields mainly the product, m. p. 241°, with a very small amount of alcohol-soluble material, m. p. 180—190°, possibly a mixture of sulphide and sulphoxide.

Experimental

2 : 2′ : 4 : 4′-Tetranitrodiphenyl sulphide was prepared by Twiss's method (*J.*, 1914, **105**, 1678) and was freed from disulphide by recrystallisation from glacial acetic acid. The pure sulphide had m. p. 196° (Found : S, 8·7; 8·8. Calc. for $C_{12}H_6O_8N_4S$: S, 8·7%).

2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphoxide.*—(*a*) *Hydrogen peroxide oxidation.* 2 : 2′ : 4 : 4′-Tetranitrodiphenyl sulphide (2·0 g.) was boiled in glacial acetic acid (50 ml.) under reflux, while hydrogen peroxide (25 ml.; 100-vol.) was added during 1 hour. On cooling, very pale yellow prisms separated and, recrystallized from acetone, had m. p. 241° (yield, almost 100%).

(*b*) *Nitric acid oxidation.* The sulphide (10 g.) was slowly added to cold nitric acid (*d* 1·52; 25 ml.). On warming, the sulphide dissolved. The solution was refluxed for 2 hours, cooled, and poured into a large bulk of ice-water; the precipitate, washed free from acid and recrystallized from acetone, had m. p. 241° (Found : S, 8·3, 8·4. Calc. for $C_{12}H_6O_9N_4S$: 8·4%).

2 : 2′ : 4 : 4′-*Tetranitrodiphenyl Sulphone.*—(*a*) *Chromium trioxide oxidation of the sulphide.* To a boiling solution of the sulphide (5·0 g.) in glacial acetic acid (150 ml.) chromium trioxide

(20 g.) was added in small portions. Refluxing was continued for 6 hours, and the solution poured into a large bulk of water; the precipitate, washed free from chromium compounds and recrystallized from aqueous acetone, had m. p. 174—175°.

(*b*) *Dichromate–sulphuric acid oxidation of the sulphide.* The sulphide (2 g.) was added to sulphuric acid (*d* 1·84; 10 ml.), potassium dichromate (2 g.), and water (2 ml.). The whole was warmed to *ca.* 120° and kept thereat for 20 min. with frequent shaking. On cooling and pouring of the mixture into ice-water the *sulphone* separated in fine crystalline form, was washed free from chromium salts, and recrystallized from aqueous acetone; it had m. p. 174—175° (yield, almost 100%) (Found: S, 8·05, 8·1. $C_{12}H_6O_{10}N_4S$ requires S, 8·0%). It is insoluble in water, sparingly soluble in acetic acid, readily soluble in acetone, and easily decomposed by alkali.

Quantitative Oxidation of Sulphide and Sulphoxide.—Very finely powdered sulphide (0·183 g., 0·0005 mole) or sulphoxide (0·191 g., 0·0005 mole) was refluxed in all an-glass apparatus with 25 ml. of a solution of potassium dichromate in aqueous sulphuric acid [10 g. of potassium dichromate, 555 ml. of water and 444 ml. of sulphuric acid (*d* 1·84)] with frequent shaking, for 0·5—3 hours. Control solutions of sulphone (0·199 g., 0·0005 mole) in 25 ml. of the dichromate–sulphuric acid were refluxed for the corresponding periods, at the end of which both test and control solutions were diluted with water to about 150 ml. and the residual dichromate was determined with potassium iodide and thiosulphate.

The solid precipitated from the test portions was recovered and crystallized from aqueous acetone. Except in the case of the half-hour period where oxidation was visibly incomplete, the product had m. p. 174—175°.

College of Technology, Liverpool. [*Received, December 2nd,* 1952.]

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238. *Mannose-containing Polysaccharides. Part III.* The Polysaccharides in the Seeds of* Iris ochroleuca *and* I. sibirica.

By P. Andrews, L. Hough, and J. K. N. Jones.

The polysaccharides isolated from *I. ochroleuca* and *I. sibirica* seeds were found to be very similar. Each was composed of D-glucose and D-mannose in approximately equal amounts, and D-galactose (*ca.* 3%). Examination of the methylated polysaccharides showed that they were composed of chains of glucose and mannose units linked through $C_{(1)}$ and $C_{(4)}$. The galactopyranose residues were linked through $C_{(1)}$ only.

The reserve polysaccharide in the rhizomes of some species of iris is starch, whilst in others it is a fructosan (irisin) (Colin and Augem, *Compt. rend.*, 1927, **185**, 475; Augem, *Rev. gén. botan.*, 1928, **40**, 456, 537, 591; *Chem. Abs.*, 1929, **23**, 634; Schulbach, Knoop, and Liu, *Annalen*, 1933, **504**, 30), which may vary in composition from species to species (Colin and Augem, *Bull. Soc. Chim. biol.*, 1928, **10**, 489). In addition, the endosperms of the ripe seeds of three species (*I. pseudacorus, I. germanica, and I. foetidissima*) are said (*idem, ibid.*, p. 822; *Chem. Abs.*, 1928, **22**, 3682; Augem, *loc. cit.*) to contain a mannoaraban, consisting of mannose 82% and arabinose 18%. These sugars were identified as mannose phenylhydrazone and arabinosazone, m. p. 147° (lit., m. p. 160°), respectively, and their proportions were deduced from the optical rotation ($[\alpha]_D$ +31°) of iris endosperm hydrolysates; arabinose was also determined colorimetrically (as pentose). Other sugars were not detected. It was of interest to investigate further the possible occurrence of this material, since no polysaccharide composed entirely of these two sugars has yet been examined in detail. An investigation of the seeds of two species of iris (*I. ochroleuca* and *I. sibirica*) was therefore undertaken, but no mannoaraban could be detected, the seeds containing very little arabinose.

The iris seed consists of a hard horny endosperm, 2—3 mm. in diameter, covered by a brown wrinkled testa. Extraction of the endosperms of the two species of iris with 10% aqueous sodium hydroxide yielded thick mucilaginous solutions from which the polysaccharides were precipitated with alcohol. Like other neutral mannose-containing polysac-

* This paper was read in abstract at the XIIth International Congress of Pure and Applied Chemistry, New York, September, 1951. Part II, *J.*, 1952, 2744.

charides so far examined, they formed insoluble copper complexes, thus providing a method of purification. The two polysaccharides showed a striking resemblance to one another; *e.g.*, both contained D-glucose and D-mannose in the main (*ca.* 1 : 1; 97%) and a little (3%) D-galactose, and the optical rotations of the polysaccharides and of their acetyl and methyl derivatives were similar. Several precipitations of the *I. sibirica* polysaccharide as its copper complex caused no appreciable change in its composition, and as starch was absent it is likely that the material is one polysaccharide compounded of the three hexoses.

An examination of the methyl sugars produced by fission of the methylated polysaccharides also suggested that the polysaccharides were similar in structure. The trimethyl fraction accounted for about 93% (on a molecular basis) of the total methyl sugar mixture in both cases, and consisted of equal parts of 2 : 3 : 6-trimethyl D-glucose and 2 : 3 : 6-trimethyl D-mannose. Such a mixture would have $[\alpha]_D$ +32°, and approximately this value was found for both the trimethyl fractions. The tetramethyl fractions formed 3·7% (*I. ochroleuca*) and 3·2% (*I. sibirica*) of the total methyl sugars, and consisted largely of 2 : 3 : 4 : 6-tetramethyl D-galactose, thus accounting for all the galactose found in the original polysaccharides. Very small amounts of tetramethyl glucose and tetramethyl mannose were also detected. This evidence suggests that D-galactose forms the majority of the end-groups in the polysaccharides, but that there are also a small number of glucose and mannose end-groups. Whether these represent end-groups present in the original polysaccharides, or whether they were produced during isolation of the polysaccharides is unknown. Small amounts (*ca.* 3%) of dimethyl sugars were present, but none was identified : probably they arose in part from incomplete methylation of the polysaccharides, but they may also represent points of branching.

The possibility that the polysaccharides are mixtures is compatible with the evidence available. Thus, the galactose end-group may have arisen from the presence of a small amount of galactomannan (cf. Parts I and II), which would also give an insoluble copper complex; in this case the iris polysaccharides were mixtures of glucomannan with a small proportion of galactomannan. However, in view of the similarity, especially in composition, between the two iris polysaccharides, we tend to the view that they are not mixtures. On the above evidence and the assumption that all the sugar residues are in the pyranose form, the polysaccharides appear to consist of chains of D-glucose and D-mannose units linked glycosidically, in a sequence as yet undetermined, through positions 1 and 4, and terminated at the non-reducing ends largely by D-galactopyranose residues, a small number being terminated by glucopyranose and mannopyranose units.

The amount of end-group as determined by the methylation procedure corresponds to repeating units of 25 and 30 hexose residues for the *I. ochroleuca* and *I. sibirica* polysaccharides respectively, whilst one molecule of formic acid is produced from 19 and 12 hexose residues respectively when the polysaccharides are oxidised with potassium metaperiodate. In the case of a linear polysaccharide composed of x sugar units, including a reducing end-group, the methylation results will give a repeating unit of x sugar units, whereas on oxidation of the unmethylated polysaccharide with periodate, one molecule of formic acid will be produced per $x/3$ sugar units. If the polysaccharide of x units possesses n points of branching, these figures are $x/(n + 1)$ and $x/(n + 3)$ respectively. The values become more nearly equal, the greater the degree of branching of the polysaccharide. Consideration of the results with the two iris polysaccharides suggests that the *I. ochroleuca* polysaccharide is of the branched-chain type (with, apparently, an average of five or six branches per molecule and a degree of polymerisation of 150—175 hexose units), whereas the *I. sibirica* polysaccharide may be linear, or branched very infrequently, and have a smaller molecular weight. However, since the original polysaccharides were isolated by extraction with warm 10% sodium hydroxide solution, and the effect of this procedure on the reducing ends of the polysaccharide molecules is unknown, the exact significance of the periodate results is uncertain. This is especially true with the *I. sibirica* polysaccharide because of the difficulty of determining the end-point of this oxidation. In this case, the conditions of oxidation were altered to obtain a solution of the polysaccharide. It is unlikely that at the pH of the oxidation (*ca.* 5), complex formation due to the presence of sulphate ions would interfere with the normal course of the oxidation [cf. however, Bell,

Palmer, and Thomas (*J.*, 1949, 1536), who found differences from the normal reaction when the oxidation was carried out in the presence of sulphate and under alkaline conditions]. The estimates of the degree of polymerisation of the two iris polysaccharides, by their reducing power, indicate that the *I. ochroleuca* polysaccharide has a considerably greater molecular weight than the other, but the values obtained bear no clear relation to the methylation and periodate results, and in any case they must be considered unreliable (cf. Lansky, Kooi, and Schoch, *J. Amer. Chem. Soc.*, 1949, **71**, 4066) because they vary with the conditions used [but compare the results of Chanda, Hirst, Jones, and Percival (*J.*, 1950, 1289) with esparto xylan] and because of the uncertain nature of the reducing end-groups of the polysaccharides. The possibility of a difference in the molecular weights of the two polysaccharides may be supported by the fact that, although they are both soluble in dilute alkali, the *I. ochroleuca* polysaccharide is precipitated when the solution is neutralised, whilst the other is not.

It is possible that some of the formic acid produced by periodate oxidation of the polysaccharides arises from hexose units linked through $C_{(1)}$ and $C_{(6)}$ only. Calculation shows that if all the formic acid arises from such sugar units, the maximum amount of 2 : 3 : 4-trimethyl hexose obtained by hydrolysis of the methylated polysaccharides would be 5% and 8·5% for the *I. ochroleuca* and *I. sibirica* polysaccharides respectively. However, no evidence for any trimethyl hexoses other than the 2 : 3 : 6-derivatives of glucose and mannose was obtained by chromatography of the eluates from the hydrocellulose column, or otherwise. It is evident that an exact determination of the degree of branching of these polysaccharides cannot yet be made by chemical means, and that molecular-weight determinations by physical means will be required.

To summarize, the polysaccharides isolated from the two species of iris seeds resemble one another closely, but may not be identical. They differ from the galactomannans (Parts I and II) in that they do not possess a highly branched structure. However, in both types of polysaccharide all the galactose units are present as end groups, and the methylated polysaccharides yield 2 : 3 : 6-trimethyl D-mannose as one of the products of hydrolysis.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper by the descending method (Partridge, *Biochem. J.*, 1948, **42**, 238). The following solvent systems were used, (*c*) being used for methylated sugars only: (*a*) *n*-butanol–ethanol–water (40 : 11 : 19; v/v) (*b*) ethyl acetate–acetic acid–water (9 : 2 : 2; v/v); (*c*) benzene–ethanol–water (169 : 47 : 15; v/v; top layer clarified with ethanol). For further details see Part II (*loc. cit.*). Ammoniacal silver nitrate and *p*-anisidine hydrochloride sprays were used.

Hydrolyses were performed with N-sulphuric acid at 95—100°, unless otherwise stated, and solutions were concentrated under reduced pressure. Optical rotations were determined at 18°. The analyses were carried out by Mr. W. Eno, Bristol.

Extraction of the Polysaccharides.—The whole seeds were reduced to coarse powders by milling, whereupon most of the broken seed-coats could be removed by flotation in water. Chromatography (solvent *b*) showed that the sugars produced by hydrolysis of the endosperm for 16 hours were mainly glucose and mannose, in approximately equal amounts, with much smaller amounts of galactose, arabinose, and xylose.

The endosperms were unaffected by boiling water, but with hot aqueous alkali they formed a gelatinous mass which partly dissolved to give a viscous brown solution. A quantity of each polysaccharide was prepared as follows: The milled seed (60 g.) was extracted for 3 hours at 50° with 2% sodium sulphite solution (2 × 1 l.) and then with water at 70—80° until the extracts were nearly colourless. The aqueous layer was decanted each time, thus removing most of the broken seed-coats. The residual endosperms were then extracted with sodium hydroxide solution (10% w/v; 3 × 800 c.c.) at *ca.* 50°, with frequent stirring. The viscous supernatant extracts were isolated on the centrifuge, combined, and poured into alcohol (2 vols.). The precipitate, which contained protein, was washed with aqueous alcohol until the washings were colourless, and dissolved in warm N-sodium hydroxide, from which solution the polysaccharide copper complex was precipitated by the slow addition, with continuous stirring, of Fehling's solution (50 c.c.). After regeneration with ice-cold 0·5N-hydrochloric acid (cf. Part II), the polysaccharide was twice precipitated with alcohol from its solution in dilute alkali, then washed

with alcohol, acetone, and ether, and dried under reduced pressure. The two polysaccharides so obtained had the following properties.

Polysaccharide from	Yield (%) from whole seed	$[\alpha]_D$ (in 2N-NaOH)	N (%)	Sulphated ash (%)
I. ochroleuca	20	$-25° \pm 2°$ (*c*, 0·7)	0·1	3·1
I. sibirica	18	$-26° \pm 3°$ (*c*, 0·7)	0·3	4·7

The *I. sibirica* polysaccharide (material A) was four times precipitated from alkaline solution with Fehling's solution, the polysaccharide being regenerated after each precipitation with ice-cold 0·5N-hydrochloric acid. The product (B) (Found: sulphated ash, 1·1%) was used in the following experiments.

The polysaccharides were both buff-coloured powders, which swelled, but failed to dissolve, in water. They formed solutions in dilute alkali which, after neutralisation with sulphuric acid, did not give a blue colour with iodine solution. The *I. ochroleuca* polysaccharide was slowly precipitated in a gelatinous form when its solution in alkali was neutralised.

Hydrolysis of the Polysaccharides.—Heating the polysaccharides at 100° with dilute acid resulted in their incomplete hydrolysis. More complete hydrolysis was effected with formic acid: the polysaccharide (0·5 g.) was dissolved in anhydrous formic acid (30 c.c.), water (5 c.c.) was added, and the solution heated at 100° for 12 hours. It was then concentrated to a syrup, which was heated with acid (5 c.c.) for 1 hour to hydrolyse any formyl esters, neutralised (Amberlite IR-4B ion-exchange resin), and concentrated.

The resultant sugar mixtures were chromatographed on hydrocellulose (22 × 2 cm.) as described by Hough, Jones, and Wadman (*J.*, 1949, 2511), with *n*-butanol half saturated with water as the mobile phase. The same sugars were isolated in each case ($[\alpha]_D$'s are equil. values in water): From *I. ochroleuca* polysaccharide, D-glucose, m. p. 146°, $[\alpha]_D$ +51·6°, D-mannose, m. p. 132°, $[\alpha]_D$ +14·5°, and galactose 1-methyl-1-phenylhydrazone, m. p. 185°; from *I. sibirica* polysaccharide, D-glucose, m. p. 146°, $[\alpha]_D$ +51°, D-mannose, m. p. 132°, $[\alpha]_D$ +14°, and galactose 1-methyl-1-phenylhydrazone, m. p. 186° (mixed m. p.s of all these compounds with authentic specimens showed no depression). The galactose derivatives (later identified as D, see below) were each isolated from mixtures of galactose and glucose; after being warmed with dilute hydrochloric acid, each yielded a sugar which was indistinguishable from galactose on the paper chromatogram.

For quantitative analyses, the polysaccharides (*ca.* 50 mg.) were hydrolysed with 90% formic acid (3 c.c.) as above; ribose was added to the hydrolysates, which after dilution with water to 30 c.c. were concentrated to small volumes and any formyl esters hydrolysed with acid. After neutralisation (Amberlite IR-4B resin), the solutions were concentrated to syrups, which were separated into their components by partition chromatography on sheets of filter-paper by elution with solvent system (*a*) for *ca.* 90 hours. After extraction from the papers, the sugars were estimated by the periodate oxidation method of Hirst and Jones (*J.*, 1949, 1659).

To the hydrolysate of the *I. ochroleuca* polysaccharide (48·0 mg.) was added ribose (20·0 mg.) (Found: galactose + glucose, 1·84, 1·19; mannose, 1·835, 1·18; ribose, 1·55, 0·975 mg.). If complete recovery of the ribose is assumed, these results indicate that hydrolysis of the polysaccharide yielded: galactose + glucose, 21·4, 22·0, and mannose, 21·3, 21·9 mg. (calc. as $C_6H_{10}O_5$). The ratio (galactose + glucose) : mannose is thus very close to 1 : 1. In another experiment, the chromatograms were irrigated with solvent (*a*) for 8 days, in order to separate the galactose and glucose, during which time the ribose was lost off the bottom of the paper (Found: galactose, 0·195, 0·15; glucose, 2·75, 2·04; mannose, 2·99, 2·22 mg.). The corresponding ratios of these three sugars are 1·0 : 14·1 : 15·3 and 1·0 : 13·6 : 14·8.

To hydrolysates of the *I. sibirica* polysaccharide [(A) 56·2, and (B) 60·4 mg.] was added ribose (17·2 and 21·4 mg. respectively) [Found for (A): galactose, 0·23, 0·17; glucose, 4·69, 3·74; mannose, 4·82, 4·02; ribose 2·92, 2·31 mg. For (B): galactose, 0·26, 0·19; glucose 5·75, 4·05; mannose, 5·86, 4·36; ribose, 4·23, 3·04 mg.]. Again on the assumption of complete recovery of the ribose, these results correspond to the production of: From (A): galactose, 1·22, 1·14; glucose, 24·9, 25·0; mannose, 25·5, 26·9 mg. (total recovery, 92, 94%), and from (B): galactose, 1·18, 1·21; glucose, 26·2, 25·7; mannose, 26·7, 27·6 mg. (total recovery 90, 90%) (sugars calc. as $C_6H_{10}O_5$). The figures represent average galactose : glucose : mannose ratios of, for (A): 1·0 : 21·2 : 22·3; for (B), 1·0 : 21·7 : 22·7.

Acetyl and Methyl Derivatives.—For acetylation, the polysaccharides (0·5 g.) were each dissolved in cold anhydrous formic acid (20 c.c.), and the viscous solutions added dropwise to ice-cold mixtures of pyridine (100 c.c.) and acetic anhydride (50 c.c.). When reaction had

ceased, the precipitates were filtered off and reacetylated at 100° with pyridine (50 c.c.) and acetic anhydride (50 c.c.). The materials dissolved slowly, and after 2 hours the solutions were poured on ice. The precipitates were soluble in acetone only after another similar acetylation (yield, *ca.* 0·4 g. in each case).

For methylation, the *I. ochroleuca* polysaccharide (4 g.) was dissolved in sodium hydroxide solution (40% w/v; 120 c.c.), and methyl sulphate (100 c.c.) added dropwise with continuous stirring and cooling. Next morning more sodium hydroxide (200 c.c.) and methyl sulphate (200 c.c.) were added. When the reaction had ceased, the solution was neutralised with acetic acid, dialysed to remove the inorganic material, and concentrated to *ca.* 50 c.c. Acetone (50 c.c.) was added, and the methylation continued by the alternate additions (3 times) of sodium hydroxide (40 g.) and methyl sulphate (90 c.c.) at room temperature. Inorganic material was then removed by dialysis, and the resulting clear aqueous solution extracted with chloroform. Evaporation of the chloroform left the methylated polysaccharide (2·8 g.), which was dissolved in methyl iodide (25 c.c.), and the solution boiled under reflux overnight with silver oxide (10 g.). The isolated product (2·7 g.; OMe, 42·2%) was further treated with Purdie's reagent. A portion (2·2 g.) of the product was fractionated by extraction with boiling mixtures of chloroform and light petroleum (b. p. 40—60°): the main fraction, a crisp yellow solid (1·86 g.), was soluble in 80%, but insoluble in 90% light petroleum.

The *I. sibirica* polysaccharide (5·5 g.) was methylated similarly. After eight methylations the chloroform-soluble product (4·7 g.) was fractionated as above, giving mainly one fraction (4·2 g.), soluble in 80%, but insoluble in 90%, light petroleum (b. p. 40—60°).

The acetyl and methyl derivatives are compared in the following Table.

Polysaccharide from	Acetyl derivative		Methyl derivative	
	Acetyl (%)	$[\alpha]_D$ (in $COMe_2$)	OMe (%)	$[\alpha]_D$ (in $CHCl_3$)
I. ochroleuca	42·5	−14° (*c*, 1·0)	43·3	−9° (*c*, 1·1)
I. sibirica	43·1	−13° (*c*, 1·2)	43·5	−11° (*c*, 1·4)

Hydrolysis of the Methylated Polysaccharides.—A solution of the methylated *I. ochroleuca* polysaccharide (0·97 g.) in methanolic hydrogen chloride (2% w/w; 30 c.c.) was boiled under reflux for 12 hours, neutralised with a slurry of silver carbonate in methanol, and filtered, and the filtrate concentrated to a syrup. The methylglycosides were hydrolysed at 100° in N-hydrochloric acid (30 c.c.) for 16 hours. After neutralisation (silver carbonate) the solution was filtered and hydrogen sulphide passed in, to remove silver ions; since the sulphide so formed could not be filtered off, the solution was concentrated to a small volume and acetone (20 c.c.) added. The precipitate was filtered off and washed with hot acetone, and the filtrate and washings were combined and concentrated to a syrup (0·93 g.).

Similarly, the methylated *I. sibirica* polysaccharide (1·54 g.) yielded a syrupy mixture of reducing sugars (1·44 g.) with $[\alpha]_D$ +30° ± 3° (*c*, 1·0 in H_2O).

Separation of the Methylated Sugars.—Paper chromatographic examination indicated that each mixture consisted mainly of trimethyl hexose, which gave only one spot (R_G 0·89, solvent *a*), and was indistinguishable from both 2 : 3 : 6-trimethyl glucose and 2 : 3 : 6-trimethyl mannose. The small amount of end group corresponded to 2 : 3 : 4 : 6-tetramethyl galactose (R_G 0·96), whilst the dimethyl hexose gave an elongated spot and appeared to be a mixture.

The methyl sugar mixtures were fractionated by partition chromatography on cellulose (28 × 4 cm.), with solvent (*c*) as the mobile phase (for details, see Part II, *loc. cit.*). Evaporation of appropriate parts of the eluate gave three syrupy fractions in each case, which were purified by dissolution in water, acetone, and ether (or acetone–ether), with intermediate filtration and evaporation, and dried.

The *I. ochroleuca* mixture of methyl sugars (0·84 g.) gave the following fractions:

Fraction (1) (39 mg.) (Found: OMe, 50·8. Calc. for tetramethyl hexose, $C_{10}H_{20}O_6$: OMe, 52·5%) gave two spots of unequal intensity on the chromatogram (R_G 0·95 and 1·00). These materials were separated on a sheet-paper chromatogram, by using solvent (*c*) and there were obtained:

Fraction (1*a*) (28 mg.) (R_G 0·95), with $[\alpha]_D$ +100° (*c*, 0·6 in H_2O). When boiled with aniline in alcohol it gave *N*-phenyl-D-galactopyranosylamine tetramethyl ether (10 mg.), m. p. and mixed m. p. 189°, $[\alpha]_D$ +37° (equil. value, *c*, 0·5 in $COMe_2$).

Fraction (1*b*) (4 mg.) (R_G 1·00). Partial demethylation was achieved with hydrobromic acid (48% w/w; 1 c.c.) at 100° for 10 min. (Hough, Jones, and Wadman, *J.*, 1950, 1702). The products included both glucose and mannose (by paper chromatography), indicating that the fraction consisted of tetramethyl glucose and tetramethyl mannose.

Fraction (2) (710 mg.) (Found: OMe, 41·7. Calc. for trimethyl hexose: OMe, 41·9%) had

$[\alpha]_D$ +34° (*c*, 1·2 in H_2O) and gave only one spot (R_G 0·89) on the chromatogram. A portion (*ca.* 0·3 g.) was dissolved in ether, and the solution seeded with 2 : 3 : 6-trimethyl D-glucose. After 7 days at 0° 30 mg. of this sugar had crystallised, which after recrystallisation from ether had m. p. and mixed m. p. 120°, and $[\alpha]_D$ +95° (initial)→+70° (equil. value; *c*, 0·7 in H_2O) $[\alpha]_D$ −40° (equil. value; *c*, 0·5 in 1% methanolic hydrogen chloride) (Found : OMe, 41·1. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). The mixture from which this sugar crystallised was oxidised with bromine water in the usual way. Attempts to crystallise 2 : 3 : 6-trimethyl D-mannonolactone from the resultant syrup were unsuccessful. Accordingly it was boiled with an alcoholic solution of phenylhydrazine, whereupon crystalline 2 : 3 : 6-trimethyl D-mannonic acid phenylhydrazide (52 mg.) was produced, which after recrystallisation from ethanol, had m. p. and mixed m. p. 132°, $[\alpha]_D$ −18° (*c*, 0·7 in H_2O) (Found : N, 8·4. Calc. for $C_{15}H_{24}O_6N_2$: N, 8·5%). The residual mixture of phenylhydrazides gave another small crop of the above phenylhydrazide, but then could not be induced to crystallise further.

Fraction (3) (42 mg.) (Found : OMe, 28·3. Calc. for dimethyl hexose : OMe, 29·8%), when examined on the paper chromatogram, appeared to contain at least three compounds which were incompletely separated from each other. Comparison with authentic samples indicated that the 2 : 3-dimethyl derivatives of glucose and mannose might be present in the fraction, and demethylation of a portion yielded both these parent sugars. No crystalline derivatives could be isolated from this fraction.

The *I. sibirica* methyl sugar mixture (1·14 g.) gave the following fractions :

Fraction (1′) (38 mg.) (Found : OMe, 50·9%) had $[\alpha]_D$ +97° (*c*, 0·8 in H_2O). It contained only *ca.* 5% of material with R_G 1·0; the remainder had R_G 0·95. When boiled with alcoholic aniline it yielded *N*-phenyl-D-galactopyranosylamine tetramethyl ether (20 mg.), m. p. and mixed m. p. 188°, $[\alpha]_D$ +38° (equil. value; *c*, 0·6 in $COMe_2$).

Fraction (2′) (960 mg.) (Found : OMe, 40·7%) had $[\alpha]_D$ +32° (*c*, 4·4 in H_2O). A portion (*ca.* 20 mg.) was oxidised in 0·2M-sodium metaperiodate solution (5 c.c.) for 18 hours; the product, isolated by continuous extraction with ether, contained no 2 : 3 : 5-trimethyl arabinose (by paper chromatography), indicating that this fraction did not contain the 3 : 4 : 6-trimethyl derivatives of glucose and mannose. A portion (*ca.* 350 mg.), dissolved in ether, gave, when seeded, 2 : 3 : 6-trimethyl D-glucose (34 mg.); after recrystallisation from ether it had m. p. and mixed m. p. 122° and $[\alpha]_D$ +91° (initial value)→+69° (equil. value; *c*, 0·6 in H_2O) [Found : OMe, 41·3. Calc. for $C_6H_9O_3(OMe)_3$: OMe, 41·9%]. A further portion of the syrup (230 mg.) was oxidised with bromine water, and the syrupy lactones boiled with alcoholic phenylhydrazine. Crystalline 2 : 3 : 6-trimethyl D-mannonic acid phenylhydrazide (50 mg. in two crops), m. p. and mixed m. p. 132°, $[\alpha]_D$ −17° (*c*, 0·6 in H_2O), but no other crystalline material was isolated from the reaction mixture.

Fraction (3′) (20 mg.) (Found : OMe, 28·8%) had $[\alpha]_D$ +24° (*c*, 0·4 in H_2O); it gave an elongated spot on the chromatogram, and consisted of derivatives of glucose and mannose, since both these sugars were produced on demethylation with hydrobromic acid; it was not further examined.

Quantitative Examination of the Methyl Sugar Mixtures.—The relative amounts of tetra-, tri-, and di-methyl sugars were estimated, after chromatographic separation on filter-paper with solvent (*c*), by the alkaline hypoiodite method (Hirst, Hough, and Jones, *J.*, 1949, 928; Jones, *J.*, 1950, 3292). 1 c.c. of 0·1N-iodine was used for the tetra- and di-, and 5 c.c. for the tri-methyl fractions; oxidation was allowed to proceed for 17 hours and the excess of iodine was titrated, after acidification, with 0·01N-sodium thiosulphate. The results are given in the following Table.

Polysaccharide from	Consumption of 0·01N-I_2 (c.c.)			Corresponding mol. ratios		
	"Tetra"	"Tri"	"Di"	"Tetra"	"Tri"	"Di"
I. ochroleuca	0·68, 0·77	15·7, 20·0	0·90, 1·06	1·0, 1·0	23, 26	1·3, 1·4
I. sibirica	1·06, 0·82	28·3, 26·8	0·92, 0·62	1·0, 1·0	27, 33	0·9, 0·8

Periodate Oxidation.—The *I. ochroleuca* polysaccharide was oxidised with potassium periodate, as described by Brown, Halsall, Hirst, and Jones (*J.*, 1948, 28). The finely powdered material (0·485 g.) was heated with water (25 c.c.) at 70—80° for 5 hours; this softened it, but it showed no signs of dissolving. The suspension was cooled, and water (50 c.c.), potassium chloride (3 g.), and 0·36N-sodium metaperiodate (25 c.c.) were added, bringing the pH to *ca.* 5. The mixture was kept in the dark, and frequently shaken. At intervals, portions (5 c.c.) of the clear supernatant liquid were withdrawn, ethylene glycol (2 c.c.) added, and the formic acid titrated with 0·0109N-sodium hydroxide : a control experiment, containing no polysaccharide, was run concurrently [Found (titres of 0·0109N-alkali corrected for blank) : 0·47 (96 hr.), 0·56 (147 hr.),

0·63 (240 hr.), 0·74 (342 hr.), 0·75 c.c. (504 hr.)]. The reaction was apparently complete after 342 hours, but none of the polysaccharide had dissolved. The total yield of formic acid, including that withdrawn for estimation, was 14·4 c.c. of 0·0109N, which corresponds approximately to the formation of one molecule of formic acid from every 19 hexose units.

Oxidation of the *I. sibirica* polysaccharide was carried out as follows. In order to obtain a solution, it (0·186 g.) was dissolved in potassium hydroxide solution (*ca.* 0·1N; 15 c.c.) and the solution brought to pH 7 with 0·1N-sulphuric acid. Potassium sulphate (2 g.) and 0·36N-sodium metaperiodate (18·8 c.c.) were added, giving a total volume of 50 c.c. and a final pH of *ca.* 5. The mixture was kept in the dark, and frequently shaken. At intervals, portions (5 c.c.) of the clear solution were withdrawn, and the formic acid content was determined in the usual way [Found (titres of 0·01N-alkali): 1·32 (190 hr.), 1·53 (284 hr.), 1·80 c.c. (452 hr.)]. Extrapolation to zero time gives a titre of 0·95 c.c., corresponding to a yield of one molecule of formic acid from every 12 hexose residues.

The oxidised polysaccharides were recovered and hydrolysed, and the products examined on the paper chromatogram. The *I. ochroleuca* polysaccharide gave traces of glucose and mannose, and the *I. sibirica* polysaccharide gave traces of one sugar, possibly glucose.

Reducing Power of the Polysaccharides.—In order to remove any traces of alcohol from them, water (30 c.c.) was added to each polysaccharide (*ca.* 1 g.), and the mixtures were evaporated to dryness (thrice). The materials were then dried at 100°/20 mm. for 5 hours. Reducing power was estimated by the alkaline hypoiodite method (Chanda *et al.*, *loc. cit.*). The polysaccharides (50—100 mg.) were treated as follows: (*a*) the sample was dissolved in 2N-sodium hydroxide (5 c.c.), and 0·1N-iodine (1 or 2 c.c.) added; mixtures were kept in the dark for 17 and 41 hours respectively, then acidified with 2N-sulphuric acid (10 c.c.); (*b*) the sample was dissolved in 2N-sodium hydroxide (2 c.c.), and 2N-sulphuric acid (1·8 c.c.), sodium hydroxide–phosphate buffer (pH 11·4) (Ingles and Israel, *J.*, 1948, 810) (4 c.c.), and 0·1N-iodine (2 c.c.) were added; after 17 hours, the mixtures were acidified with 2N-sulphuric acid (5 c.c.). In all cases, the liberated iodine was titrated with 0·01N-sodium thiosulphate. The results corresponded to the presence of one reducing group per (*a*) 20—24 and (*b*) 55—65 hexose residue in the *I. ochroleuca* polysaccharide, and per (*a*) 13—14 and (*b*) 22—23 hexose residues in the *I. sibirica* polysaccharide.

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239. *The Chemistry of Extractives from Hardwoods. Part XII.* The Cyclitols and Steroids of Opepe* (Sarcocephalus diderrichii).

By F. E. KING and L. JURD.

*meso*Inositol, and an optically active *O*-methyl*meso*inositol (yield 3·5%) possibly identical with bornesitol from Borneo rubber, are present in aqueous and alcoholic extractives of opepe, the wood of *Sarcocephalus diderrichii*. Among the constituents isolable with light petroleum are "β"-sitosterol and the previously unknown "β"-sitosteryl palmitate.

THE West African tree *Sarcocephalus diderrichii* de Wild (family *Rubiaceae*) produces a hard, golden-yellow wood, opepe, which is a valuable commercial timber, and is reported to be highly resistant to wood-rotting fungi and to certain marine parasites. There is no record of a chemical examination of the wood; toxic reactions attributed to it by Harvey-Gibson (*Biochem. J.*, 1906, **1**, 39) were subsequently shown to be due to the somewhat similar "Knysna boxwood" from *Gonioma kamassi*, family *Apocynaceae* (*idem, ibid.*, 1912, **6**, 127).

The oil isolated from the powdered wood with boiling light petroleum gave when fractionally precipitated from organic solvents a crystalline product, $C_{45}H_{80}O_2$ (0·01% of the wood), and a solid, m. p. 77—78°, the latter, however, in amounts too small for identification. From the more soluble residue were obtained a phytosterol, m. p. 135°, and a second alcohol, m. p. 184°, apparently a triterpene derivative. The alcohol, m. p. 184°, gave an acetate, benzoate, and *p*-nitrobenzoate, but the amount available was

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insufficient for more extensive investigation; it is tentatively called sarcocephalol and may have the formula $C_{30}H_{48}O$, although it is then necessary to postulate that the compound and its acetate and benzoate were obtained as hemihydrates. The properties of the phytosterol and of four of its esters, and of three derivatives of the dihydrophytosterol, closely resemble those of "β"-sitosterol recorded by Wallis and Chakravarty (*J. Org. Chem.*, 1938, **2**, 335), Simpson and Williams (*J.*, 1937, 733), and Heilbron, Jones, Roberts, and Wilkinson (*J.*, 1941, 344).

From different samples of the wood two specimens of the compound, $C_{45}H_{80}O_2$, were obtained, their m. p.s of 83·5° and 85·5° remaining unchanged by repeated crystallisation and chromatography. When hydrolysed by alkali, each gave a neutral product which apart from its low optical rotation was in other respects indistinguishable from "β"-sitosterol, and the acidic hydrolysate, $C_{16}H_{32}O_2$, had m. p. 59° undepressed by pure palmitic acid. This compound is therefore regarded as "β"-sitosteryl palmitate, but the presence of other similar substances in the natural product is evident from the higher m. p. (88—88·5°) and from the optical rotation of the ester synthesised from authentic components.

The syrupy aqueous extract of the wood was fractionated with boiling methanol into the sparingly soluble *meso*inositol (0·37% of the wood), and a more easily dissolved crystalline product (3½%), $C_7H_{14}O_6$, from which were prepared a penta-acetate and -propionate. Zeisel analysis showed the presence of a methoxyl group, the action of boiling hydriodic acid yielding *meso*inositol. The m. p. (201—202°) and specific rotation (+31·4°) of the opepe cyclitol agree with the values (m. p. 199—203°, $[\alpha]_D$ +31·16°) found by Flint and Tollens (*Annalen*, 1892, **272**, 288) for bornesitol isolated from Borneo rubber by Girard (*Z. Chem.*, 1871, **7**, 335) who recorded m. p. 175°, $[\alpha]_D$ +32°, and it is probable that the two compounds are identical.

*meso*Inositol and the *O*-methyl*meso*inositol are likewise obtained from opepe by alcohol-extraction, a method which has also led to the isolation of an unidentified acid (0·004%). By treatment with hot aqueous hydrochloric acid traces of a yellow alkaloid have been extracted from the wood.

Experimental

The investigation covered three specimens of the wood, each identified at the D.S.I.R. Forest Products Laboratory as *Sarcocephalus diderrichii*, which were obtained through the kindness of Mr. W. O. Woodward, The Nottingham Mills Co. Similar extractives were derived from two of the specimens (A) but the third (B) differed appreciably in both the nature and the quantity of its soluble constituents.

Light Petroleum Extraction.—Specimen (A). The thick yellow oil (180 g.) extracted (Soxhlet; 20 hours) from the powdered heartwood (A) (18 kg.) by boiling light petroleum (b. p. 60—80°) was dissolved in ether (150 c.c.) and added to boiling acetone (1200 c.c.). The solution was decanted from sticky precipitate, concentrated to 800 c.c., and kept at room temperature for 15 hours, thereby giving a partly crystalline deposit (1). Further evaporation, to 300 c.c., and chilling (0°; 12 hours) yielded an unidentified pale yellow compound (0·2 g.) (2), m. p. (after 2 crystallisations from acetone) 75—76°, forming from light petroleum cream-coloured needles, m. p. 77—78° (Found: C, 77·7; H, 12·8%). The light petroleum filtrate, decolorised by passage through alumina, was evaporated and the residue obtained as needles (3), m. p. 79—80°, by crystallisation from acetone. This product and the ethyl acetate-soluble portion of (1) were combined and recrystallised from acetone, further purification in light petroleum solution by chromatography (alumina; light petroleum) giving "β"-*sitosteryl palmitate* in needles, m. p. 83·5°, $[\alpha]_D$ −7·3° (in $CHCl_3$) (Found: C, 82·7; H, 11·9. $C_{45}H_{80}O_2$ requires C, 82·75; H, 12·35%).

The oil (4) from which these compounds were separated was dissolved in ethanol (400 c.c.) containing potassium hydroxide (20 g.) and heated under reflux for 2½ hours. The alkali-insoluble part extracted by ether was purified from light petroleum solution by chromatography on alumina. Elution with benzene gave an oil which dissolved in light petroleum, yielding crystals of sarcocephalol (0·3 g.). Further elution with ether afforded "β"-sitosterol (1 g.), glistening plates, m. p. 136·5°, also obtained in a similar manner from the oil (4) before it had been subjected to hydrolysis.

Specimen (B). The oil (*ca.* 35 g.) obtained from specimen (B) (3·5 kg.) by exhaustion with

light petroleum was dissolved in ether (30 c.c.) and added to boiling acetone (250 c.c.). The solution, separated from gummy precipitate and concentrated to 200 c.c., gave clusters of needles which when purified by chromatography and crystallised from acetone gave " β "-sitosteryl palmitate (1 g.), m. p. 85·5°, $[\alpha]_D$ −7·8° (Found: C, 82·7, 82·5; H, 11·9, 12·1%).

" β "-*Sitosteryl Palmitate*.—(a) *Hydrolysis*. The ester (0·8 g.) from (B) was heated under reflux for 2 hours with potassium hydroxide (5 g.) in alcohol (160 c.c.), the neutral product, which was extracted by ether after the addition of water, crystallising from methanol in plates (0·45 g.), m. p. 135°. The ester from (A) gave a similar neutral product, m. p. 129—130°, which after 6 crystallisations from methanol had m. p. 135°, alone or mixed with that from sample (B) and with authentic " β "-sitosterol.

The aqueous alkaline solution yielded on acidification a solid crystallising from methanol in needles, m. p. 59°, and 59—59·5° when mixed with pure palmitic acid, m. p. 62·4° (Found: C, 75·3; H, 12·5. Calc. for $C_{16}H_{32}O_2$: C, 74·95; H, 12·6%).

(b) *Synthesis*. The acid chloride prepared by refluxing palmitic acid (0·2 g.), m. p. 62·4°, with thionyl chloride (2 c.c.) for 30 minutes was dissolved in benzene (2 c.c.) and mixed with β-sitosterol (0·2 g.), m. p. 137°, and pyridine (1 c.c.) and heated on a steam-bath for 30 minutes, Addition of water, extraction with ether, washing, etc., gave " β "-*sitosteryl palmitate*, forming after several crystallisations from acetone, clusters of needles, m. p. 88—88·5°, $[\alpha]_D$ −18·6° (Found: C, 82·7; H, 12·3%), and m. p. 86—87° when mixed with the ester, m. p. 85·5°, from (B).

" β "-*Sitosterol*.—(*a*) The sitosterol, m. p. 136·5°, isolated from the light petroleum extract had $[\alpha]_D$ −33° (recorded for " β "-sitosterol, −37°, and m. p.s from 135° to 137°). The low carbon analysis for " β "-sitosterol, attributed to solvation (Heilbron *et al.*, *J.*, 1941, 344), was obtained also in this work (Found: C, 82·5; H, 12·0. Calc. for $C_{29}H_{50}O$: C, 84·0; H, 12·1%). The acetate had m. p. 120—121° (Found: C, 81·2; H, 11·4. Calc. for $C_{31}H_{52}O_2$: C, 81·5; H, 11·5%) (" β "-sitosteryl acetate has m. p.s from 123·5° to 127°); the benzoate had m. p. 141° (Found: C, 83·4; H, 9·7. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5) (" β "-sitosteryl benzoate had m. p. 145—147°); the *p*-nitrobenzoate had m. p. 187° (Found: C, 76·3; H, 9·2; N, 2·6. Calc. for $C_{36}H_{53}O_4N$: C, 76·7; H, 9·5; N, 2·5%) (" β "-sitosteryl *p*-nitrobenzoate has m. p. 183—184°); and the 3 : 5-dinitrobenzoate had m. p. 207° (Found: C, 70·8; H, 8·4. Calc. for $C_{36}H_{52}O_6N_2$: C, 71·0; H, 8·6%) (" β "-sitosteryl 3 : 5-dinitrobenzoate has m. p. 202—203° or 207—209°). Reduction of the sterol in acetic acid over palladised charcoal at N.T.P. gave the stigmastanol (dihydrositosterol), m. p. 132°, characterised by the acetate, m. p. 129° (Found: C, 81·2; H, 12·0. Calc. for $C_{31}H_{54}O_2$: C, 81·5; H, 11·5%) (stigmastanyl acetate has m. p. from 128° to 130·5°), the benzoate, m. p. 135° (Found: C, 83·3; H, 11·1. Calc. for $C_{36}H_{56}O_2$: C, 83·0; H, 10·8%) (stigmastanyl benzoate has m. p. 137°), and the p-*nitrobenzoate*, m. p. 209° (Found: C, 76·7; H, 9·4. $C_{36}H_{55}O_4N$ requires C, 76·7; H, 9·5%).

(*b*) The neutral hydrolysate, m. p. 135°, of the palmitate from (A) had $[\alpha]_D$ −17·6° (Found: C, 82·6; H, 12·2%), and that from (B) had m. p. 135°, $[\alpha]_D$ −16·8° (Found: C, 82·5; H, 11·7%) but the sterols otherwise closely resembled " β "-sitosterol in the m. p. and anlyses of their acetates, benzoates, *p*-nitrobenzoates and 3 : 5-dinitrobenzoates (L. Jurd, Thesis, Nottingham, 1952).

Sarcocephalol.—After 4 crystallisations from methanol, *sarcocephalol* formed plates, m. p. 184°, $[\alpha]_D$ +40·7° [Found, after drying *in vacuo* at 140—150°: C, 83·2, 83·7; H, 11·5, 11·6; loss, 3·2%; *M* (Rast), 441, 462. $C_{30}H_{48}O,\frac{1}{2}H_2O$ requires C, 83·1; H, 11·4%; *M*, 434]. Its solution in chloroform–acetic anhydride developed with sulphuric acid a permanent pink colour. The *acetate*, from sodium acetate–acetic anhydride, crystallised from methanol in plates, m. p. 220° (Found, after drying at 100° *in vacuo*: C, 80·8; H, 11·0. $C_{32}H_{50}O_2,\frac{1}{2}H_2O$ requires C, 80·8; H, 10·8%). The *benzoate*, from pyridine–benzoyl chloride, purified in benzene by chromatography, formed shining needles, m. p. 244°, from acetone–methanol (Found, after drying at 100° *in vacuo*: C, 82·9; H, 9·8. $C_{37}H_{52}O_2,\frac{1}{2}H_2O$ requires C, 82·6; H, 9·9%). *Sarcocephalyl* p-*nitrobenzoate*, flattened rods (from acetone–methanol), had m. p. 268°, $[\alpha]_D$ +5·8° (Found, after drying at 100° *in vacuo*: C, 77·4; H, 9·2. $C_{37}H_{51}O_4N$ requires C, 77·4; H, 9·0%).

Aqueous Extraction.—Fine shavings of (A) (400 g.) were covered with water which was boiled for 30 minutes. The extraction was repeated and the united solutions were evaporated *in vacuo* to a thick syrup which was heated under reflux with methanol (400 c.c.) for 1 hour. The solid residue was further treated with boiling methanol (400 c.c.), and the two solutions were combined and kept at 0°, thus yielding a crystalline product (14·4 g.) (*X*). Extraction of (*X*) with boiling methanol (2 × 300 c.c.) left *meso*inositol (1·5 g.) which separated from aqueous ethanol in rectangular prisms, m. p. 221°. When concentrated to 250 c.c. and set aside for several days,

the methanol solution deposited the cyclitol (11·5 g.), m. p. 199—200°, and a further amount (2·6 g.), m. p. 198°, was similarly obtained by reducing the original methanol solution (800 c.c.) to 80 c.c. Recrystallisation from aqueous methanol gave pure bornesitol, $[\alpha]_D^{20}$ +31·4° (*c*, 4·213 in H_2O), m. p. 201—202°.

No crystalline compounds were obtained when an evaporated aqueous extract of the wood specimen (B) was treated with methanol. However, acetylation of the crude substance, and recrystallisation from ethanol of the ether-soluble portion of the product, gave penta-acetylbornesitol, m. p. 137—138° (see below).

meso-Inositol.—(*a*) The recrystallised compound had m. p. 221° alone or with an authentic specimen, and gave hexa-acetyl*meso*inositol, needles (from benzene–light petroleum), m. p. 215° (Found: C, 49·9; H, 5·5; OAc, 57·9. Calc. for $C_{18}H_{24}O_{12}$: C, 50·0; H, 5·6; 6OAc, 59·2%).

(*b*) Bornesitol (0·2 g.) was heated under reflux with hydriodic acid (3 c.c.; *d* 1·7) for 1 hour. Evaporation *in vacuo* yielded *meso*inositol, m. p. and mixed m. p. 221°; hexa-acetate, m. p. and mixed m. p. 215°.

Bornesitol.—The pure cyclitol, m. p. 201—202°, crystallises in rectangular prisms (Found: C, 43·5; H, 7·0; OMe, 19·3. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; 1OMe, 16·0%), very soluble in water, and moderately soluble in hot acetic acid. The *penta-acetate*, prepared with acetic anhydride–sodium acetate, is obtained in good yield (80%) only if excess of anhydride is evaporated *in vacuo* before treatment with water. Crystallisation from light petroleum gave needles, m. p. 138—139°, and either 138—139° or 157° from alcohol or benzene–light petroleum. When seeded, alcoholic solutions of the low-melting form gave the variety m. p. 157°, $[\alpha]_D^{20}$ +11·8° (*c*, 0·76 in $COMe_2$) [Found: C, 50·2; H, 6·0; OMe, 7·9; OAc, 53·7%; *M* (Rast), 425. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0; 1OMe, 7·7; 5OAc, 53·2%; *M*, 404].

The *pentapropionate*, prepared with propionic anhydride and sodium salt, crystallised from light petroleum (b. p. 40—60°) in rods, m. p. 47—48° (Found: C, 55·5; H, 7·2; OMe, 7·6. $C_{22}H_{34}O_{11}$ requires C, 55·6; H, 7·2; 1OMe, 6·5%). *Pentabenzoylbornesitol*, obtained with benzoyl chloride–pyridine, crystallised from ethanol in needles, m. p. 125—126° (Found: C, 71·2; H, 5·1. $C_{42}H_{34}O_{11}$ requires C, 70·6; H, 4·8%).

Ethyl Alcohol Extraction.—Fine shavings of the wood specimen (B) (10 kg.) were extracted with boiling ethanol (Soxhlet; 20 hours). From the cold solution (9 l.) an amorphous red solid (55 g.) separated and was discarded. Concentration to 1500 c.c. gave a semi-crystalline deposit (6 g.) (1) which was removed; when the filtrate was treated with ether (4½ l.) a yellow granular solid (205 g.) (2) was obtained. Evaporation of the ether–ethanol solution to 400 c.c. gave, after 24 hours at room temperature, a crystalline mass (3). Further concentration (to 150 c.c.) and the addition of light petroleum caused the deposition of sticky material from which the solution was decanted. Evaporation left an oil which was dissolved in a little boiling acetone, thus yielding when cold a crystalline solid (0·4 g.) (4).

By treatment of (2) with hot methanol (500 c.c.) crystalline material (14·7 g.) (5) was obtained, and the extraction of (3) with light petroleum (2 × 100 c.c.) left a residue (5·6 g.) (6). The petroleum-soluble portion was isolated and when crystallised from acetone afforded "β"-sitosteryl palmitate (1·4 g.), m. p. 83°. The combined products (1), (5), and (6) were powdered and extracted with boiling methanol (2 × 500 c.c.). The residue (5·6 g.) consisted of *meso*inositol, m. p. 221° after crystallisation from aqueous alcohol. When the methanol solution was concentrated to 300 c.c., bornesitol (17·8 g.), m. p. 200—201°, was isolated.

The highly crystalline pale yellow solid (4) was washed with warm benzene and recrystallised from a large volume of methanol, thereby forming an *acid*, in glistening cubes, m. p. 286° (Found: C, 73·0, 73·1; H, 9·0, 9·0; OMe, nil; act. H, 0·66%; equiv., 276, 273).

Acid Extraction.—The powdered wood (B) (1600 g.) was covered with 1% hydrochloric acid which was heated at 100° for 2 hours. The treatment was repeated and the combined solutions were extracted with ether. After addition of excess of ammonia to the aqueous liquid, basic material was isolated by means of ether. The yellow product was treated with light petroleum (50 c.c.), and amorphous solid removed by filtration. The filtrates concentrated to 10 c.c. deposited a further amount of amorphous substance, and after further evaporation the solution (3 c.c.) gave clusters of bright yellow prisms (50 mg.) which when recrystallised from light petroleum darkened at 182—183° and had m. p. 200° (Found: C, 74·6; H, 5·7; N, 13·3; OMe, nil%).

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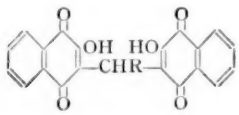
THE UNIVERSITY, NOTTINGHAM. [*Received, December 18th*, 1952.]

240. *Quinones. Part I. Chloroalkylation.*

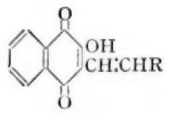
By R. H. Thomson.

1 : 4-Naphthaquinones (but not benzoquinones) may be chloroalkylated by saturating their solutions in cold acetic acid containing an aldehyde with dry hydrogen chloride. 1 : 4-Naphthaquinone gave the 2 : 3-bischloromethyl compound (V), 2-methyl-1 : 4-naphthaquinone gave the 3-derivatives (IV; R = Me; R′ = H, Me, and Ph), 2-ethyl-1 : 4-naphthaquinone gave the analogues (IV; R = Et; R′ = H and Me) and 2-chloro-1 : 4-naphthaquinone gave its 3-chloromethyl derivative (IV; R = Cl; R′ = H). The scope of the reaction appears to be limited. Yields are 50—60%. Catalytic reduction of the chloromethylquinones (except V), followed by oxidation, afforded diquinones (*e.g.*, VI).

A variety of compounds may be obtained by the reaction of aldehydes with naphthaquinones. For instance, Hooker and Carnell (*J.*, 1894, **65**, 76) prepared diquinones of type (I) by heating various aldehydes with 2-hydroxy-1 : 4-naphthaquinone in alcohol, and Hooker (*J.*, 1896, **69**, 1362; *J. Amer. Chem. Soc.*, 1936, **58**, 1163) obtained alkenylhydroxyquinones of type (II) by using a large excess of the aldehyde in hot acetic–hydrochloric acid. By the latter method Brockmann and Müller (*Annalen*, 1939, **540**, 51) obtained both alkyl- and alkenyl-naphthazarins, but 1 : 4-naphthaquinone and certain alkyl derivatives condense with equimolecular amounts of aldehydes under these conditions to give anthocyanidins of type (III) (Raudnitz and Puluj, *Ber.*, 1931, **64**, 2212; Fieser and Fieser, *J. Amer. Chem. Soc.*, 1941, **63**, 1574).



(I)



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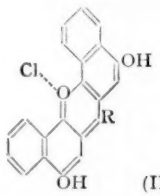
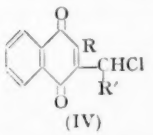


(III)

It is now found that chloroalkylquinones of type (IV) can be obtained in 50—60% yield by the interaction of aldehydes and naphthaquinones in cold glacial acetic acid in the presence of hydrochloric acid. 2-Methyl-1 : 4-naphthaquinone reacted with formaldehyde, acetaldehyde, and benzaldehyde, to give the chloroalkylquinones (IV; R = Me; R′ = H, Me, and Ph respectively) but chloroalkylation did not occur with propaldehyde, 2-formylthiophen, or 2-naphthaldehyde. In all cases the solution became red (owing to anthocyanidin formation) and when the reaction failed it was usually possible to isolate some 3-chloro-2-methyl-1 : 4-naphthaquinone from the tarry product. (The anthocyanidin and the chloromethylquinone were isolated from a blank reaction when no aldehyde was present.) 2-Ethyl-1 : 4-naphthaquinone gave chloromethyl and chloroethyl derivatives; reaction with benzaldehyde yielded a small amount of an unidentified chlorine-free compound, m. p. 280°. Although chloromethylation of 2-chloro-1 : 4-naphthaquinone proceeded smoothly, attempted reactions with acetaldehyde and benzaldehyde afforded only 2 : 3-dichloro-1 : 4-naphthaquinone in low yield. 2-Hydroxy-1 : 4-naphthaquinone did not react with aldehydes in the cold; when heated it condensed with formaldehyde to give (I; R = H) (previously obtained by Fieser *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3214, under very similar conditions) but did not condense with benzaldehyde or acetaldehyde (cf. Hooker, *loc. cit.*). 1 : 4-Naphthaquinone readily formed the bischloromethyl derivative (V) and reaction with acetaldehyde gave, in minute quantity, a chlorine-free compound which appears to be (VII); with benzaldehyde (III; R = Ph) was obtained even in the cold. Attempts to chloroalkylate benzoquinones were unsuccessful; with benzoquinone and its 2 : 5-dichloro- and 2 : 6-dimethyl derivatives, the products were mixtures of chloroquinols, and an attempt to chloromethylate chalkone produced the hydrochloride only.

Chloroalkylation is thus a limited reaction although fortunately chloromethylation, which is likely to be the most useful, is the most successful. The reaction is very similar to Hooker's (*loc. cit.*) alkenylation process which proceeds *via* an "aldol." At low temperatures a replacement reaction would give rise to a chloroalkyl group but may be succeeded, according to the conditions, by an elimination reaction to form an alkenyl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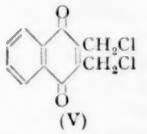
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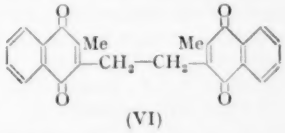
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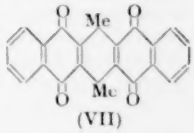
(VII)

group. This complication is absent in chloromethylation. The first step in the reaction is presumably co-ordination of carbonyl-oxygen with a proton, and hence quinone and aldehyde compete, and both chloroalkylation and hydrochloric acid addition can proceed simultaneously, the latter predominating with the more reactive benzoquinones.

Catalytic reduction of the chloroethyl and chlorobenzyl compounds proceeded smoothly in glacial acetic acid, but 2-chloro-3-chloromethyl- and 3-chloromethyl-2-methyl-1 : 4-naphthaquinone formed very insoluble precipitates (quinhydrones?) during reduction, and the ultimate yields of 2-chloro-3-methyl- and 2 : 3-dimethyl-1 : 4-naphthaquinone respectively were very poor. By working in dimethylformamide solution precipitation was avoided and diquinones (*e.g.*, VI) were obtained on subsequent oxidation. These diquinones were also formed by reaction of the chloromethylquinones with silver powder. Attempts to convert (V) into a *cyclo*butene derivative by various methods were of no avail. The products formed were apparently more complex as they did not sublime in a high vacuum.

Experimental

3-Chloromethyl-2-methyl-1 : 4-naphthaquinone.—A solution of 2-methyl-1 : 4-naphthaquinone (1 g.) in glacial acetic acid (10 c.c.) containing aqueous formaldehyde (3 c.c.; 36%) was cooled in ice-water, and dry hydrogen chloride passed in for 30 minutes. The solution became red and, after being kept overnight, blue, and was then poured on ice. The dull pink precipitate was washed with water until orange-brown and crystallised from alcohol (charcoal) in light yellow needles, m. p. 107—108° (58%). The yield was not appreciably affected by raising the temperature to 60°, increasing the time of reaction and the amount of formaldehyde, or using paraformaldehyde.

1 : 2-Bis-(2-methyl-1 : 4-naphthaquinon-3-yl)ethane.—(*a*) A suspension of silver powder (1 g.) in dry benzene (10 c.c.) containing 3-chloromethyl-2-methyl-1 : 4-naphthaquinone (0·3 g.) was refluxed for 5 hours, then filtered, and the residue extracted twice with boiling benzene. The combined filtrates were concentrated and allowed to cool. Light yellow needles, m. p. 269—270° (28%), separated. (*b*) The chloromethylquinone (0·4 g.) in dimethylformamide (15 c.c.) was hydrogenated in the presence of 2% palladised strontium carbonate (1 g.) until 1·5 mols. of hydrogen were taken up. After removal of the catalyst a solution of chromium trioxide (0·2 g.) in water (2 c.c.) was added and the mixture heated on the water-bath for 20 minutes. The suspension obtained was diluted with water and filtered. The *product* crystallised from glacial acetic acid in yellow leaflets, m. p. 269—270° (77%) (Found: C, 77·6; H, 5·1. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%). When the hydrogenation was carried out in glacial acetic acid (30 c.c.) containing anhydrous sodium acetate (0·4 g.) and with a palladised barium sulphate catalyst, a purple precipitate appeared and the hydrogen uptake was slow and incomplete. Working up as before yielded 2 : 3-dimethyl-1 : 4-naphthaquinone, m. p. and mixed m. p. 126° (70 mg.).

3-1′-Chloroethyl-2-methyl-1 : 4-naphthaquinone.—Dry hydrogen chloride was passed into a solution of 2-methyl-1 : 4-naphthaquinone (1 g.) in glacial acetic acid (10 c.c.) containing acetaldehyde (1 c.c.) for 10 minutes, with cooling in ice-water. Next morning the red solution was poured on ice, and the precipitate washed with a little cold alcohol and crystallised from the same solvent (charcoal) in yellow needles, m. p. 145—146° (55%) (Found: C, 66·7; H, 4·7. $C_{13}H_{11}O_2Cl$ requires C, 66·5; H, 4·7%). This reaction failed when concentrated hydrochloric acid was used. The *chloroethylquinone* (0·5 g.) in glacial acetic acid (20 c.c.) containing anhydrous sodium acetate (0·5 g.) was hydrogenated in the presence of 5% palladised barium

sulphate (0·1 g.). After absorption of 2 mols. of hydrogen the suspension was filtered and oxidised for 15 minutes on the water-bath with a solution of chromium trioxide (0·25 g.) in water (2 c.c.). 3-Ethyl-2-methyl-1 : 4-naphthaquinone was isolated by dilution with water. It crystallised from methanol in light yellow needles, m. p. and mixed m. p. 72—73° (82%).

3-α-*Chlorobenzyl*-2-*methyl*-1 : 4-*naphthaquinone*.—A cooled mixture of 2-methyl-1 : 4-naphthaquinone (1 g.), benzaldehyde (0·7 c.c.), and glacial acetic acid (10 c.c.) was treated with dry hydrogen chloride for 30 minutes, set aside overnight, and poured into water. The *product* crystallised from alcohol in light yellow needles, m. p. 103° (44%) (Found: C, 73·0; H, 4·5. $C_{18}H_{15}O_2Cl$ requires C, 72·8; H, 4·4%). Catalytic hydrogenation and subsequent oxidation afforded 3-benzyl-2-methyl-1 : 4-naphthaquinone, m. p. and mixed m. p. 108° (95%).

3-*Chloromethyl*-2-*ethyl*-1 : 4-*naphthaquinone*.—A cold mixture of 2-ethyl-1 : 4-naphthaquinone (1 g.), aqueous formaldehyde (3 c.c.; 36%), and acetic acid (8 c.c.) was saturated with dry hydrogen chloride for 15 minutes, and worked up next day. Crystallisation from methanol (charcoal) gave yellow needles, m. p. 86—87° (53%) (Found: C, 66·6; H, 4·5. $C_{13}H_{11}O_2Cl$ requires C, 66·5; H, 4·7%).

1 : 2-*Bis*-(2-*ethyl*-1 : 4-*naphthaquinon*-3-*yl*)*ethane*.—This was obtained from 3-chloromethyl-2-ethyl-1 : 4-naphthaquinone by (*a*) refluxing in dry benzene with silver powder, or (*b*) hydrogenation over palladised barium sulphate in glacial acetic acid–anhydrous sodium acetate, followed by chromic acid oxidation. The *diquinone* crystallised from glacial acetic acid in light yellow needles, m. p. 267° (62%) (Found: C, 78·45; H, 5·55. $C_{26}H_{22}O_4$ requires C, 78·35; H, 5·55%).

3-1′-*Chloroethyl*-2-*ethyl*-1 : 4-*naphthaquinone*.—A cooled mixture of 2-ethyl-1 : 4-naphthaquinone (1 g.), acetaldehyde (1 c.c.), and glacial acetic acid (10 c.c.) was treated with dry hydrogen chloride for 15 minutes and the *product* was isolated after 3 hours. It crystallised from methanol in yellow needles, m. p. 103° (63%) (Found: C, 67·4; H, 5·4. $C_{14}H_{13}O_2Cl$ requires C, 67·55; H, 5·4%).

2 : 3-*Diethyl*-1 : 4-*naphthaquinone*.—This was obtained from the above chloroethylquinone by catalytic hydrogenation and subsequent oxidation. The *product* was purified by vacuum-sublimation (thrice), yielding yellow needles, m. p. 72—73° (90%) (Found: C, 78·25; H, 6·5. $C_{14}H_{14}O$ requires C, 78·45; H, 6·6%).

2-*Chloro*-3-*chloromethyl*-1 : 4-*naphthaquinone*.—A mixture of 2-chloro-1 : 4-naphthaquinone (1 g.), aqueous formaldehyde (3 c.c.; 36%), and glacial acetic acid (15 c.c.) was cooled in ice-water and saturated with dry hydrogen chloride for 20 minutes. After several hours the crystals were collected and recrystallised from alcohol in lemon-yellow blades, m. p. 119° (50%) (Found: C, 54·5; H, 2·5. $C_{11}H_6O_2Cl_2$ requires C, 54·8; H, 2·5%). A little more was obtained by dilution of the reaction mixture after filtration.

1 : 2-*Bis*-(2-*chloro*-1 : 4-*naphthaquinon*-3-*yl*)*ethane*.—Prepared from 2-chloro-3-chloromethyl-1 : 4-naphthaquinone by (*a*) reaction with silver powder in boiling benzene or (*b*) hydrogenation in dimethylformamide over palladised strontium carbonate and subsequent oxidation, the *diquinone* crystallised from dimethylformamide in pale yellow leaflets, m. p. 302° (Found: C, 64·5; H, 3·1. $C_{22}H_{12}O_4Cl_2$ requires C, 64·25; H, 2·95%). When the hydrogenation was carried out in glacial acetic acid a trace of 2-chloro-3-methyl-1 : 4-naphthaquinone was isolated.

2 : 3-*Bischloromethyl*-1 : 4-*naphthaquinone*.—A cooled mixture of 1 : 4-naphthaquinone (1 g.), aqueous formaldehyde (6 c.c.; 36%), and glacial acetic acid (15 c.c.) was saturated with dry hydrogen chloride for 30 minutes. Next morning the crystals were washed with alcohol and recrystallised from the same solvent, forming stout yellow-brown needles, m. p. 142—143° (58%) (Found: C, 56·5; H, 3·0; Cl, 27·7. $C_{12}H_8O_2Cl_2$ requires C, 56·5; H, 3·15; Cl, 27·8%). By the same procedure, using acetaldehyde (1 c.c.) in place of formalin, a product was obtained which after extraction with boiling alcohol (20 c.c.) and crystallisation from glacial acetic acid (charcoal) formed yellow needles, m. p. 304° (decomp., darkening from 270°) (12 mg.) (Found: C, 77·85; H, 4·4. $C_{24}H_{16}O_4$ requires C, 78·25; H, 4·4%). The *substance* gave a negative Craven test (*J.*, 1931, 1605) and no colour on warming with Claisen's alkali.

Addition of Hydrochloric Acid to 2 : 5-*Dichlorobenzoquinone*.—A suspension of 2 : 5-dichlorobenzoquinone (1 g.) in glacial acetic acid (10 c.c.) and aqueous formaldehyde (6 c.c.; 36%) was cooled in ice-water and saturated with dry hydrogen chloride for 15 minutes. The quinone dissolved, forming an orange-red solution, the colour subsequently faded, and colourless crystals separated. These were collected (0·52 g.; m. p. 170—200°), and crystallised first from benzene and then from glacial acetic acid, forming needles, m. p. 230—232° (0·24 g.). Oxidation with chromic acid yielded chloranil, m. p. 290° (in sealed tube). Concentration of the benzene

mother-liquor gave a product, m. p. 130—140° (70 mg.), which on oxidation yielded trichlorobenzoquinone, m. p. 170°. When the addition reaction was repeated in the absence of formaldehyde the initial crop of crystals had m. p. 135° (0·75 g.) (trichloroquinol has m. p. 136°). Reactions with other benzoquinones were similar.

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241. *The Addition of Free Radicals to Unsaturated Systems. Part II*. Radical Addition to Olefins of the Type* R·CH:CH_2.

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The formation of CF_3·CH_2·CHIR and not CF_3·CHR·CH_2I by the addition of trifluoroiodomethane to R·CH:CH_2 (R = Me, Cl, F, CO_2Me, CF_3, or CN), shows that orientation in radical addition reactions does not depend on the polarisation of the double bond, but on other factors such as radical stability.

Methods for the replacement of iodine in fluoro-iodo-compounds by chlorine, bromine, or hydrogen are described, and infra-red and ultra-violet spectra are recorded.

IN attempting to determine how the direction of addition of a radical to an unsaturated system RR'C:CR''R''' is influenced by the nature of R, R', R'', and R''', olefins of the type R·CH:CH_2 have been studied. The olefins chosen (R = Me, Cl, F, CO_2Me, CN, and CF_3) show a wide range of reactivity to electrophilic and nucleophilic attack by reagents A^+B^-, each yielding substantially one product. The direction of addition of A^+B^- is not the same in each case: some give CHRA·CH_2B, others CHRB·CH_2A. For addition to R·CH:CH_2, inductive and hyperconjugation effects are operative when R = Me, induction and back-co-ordination must be considered when R = Cl or F, and when R = CO_2Me or CN effects due to induction and conjugation may be of importance.

The direction of addition of the trifluoromethyl radical derived from trifluoroiodomethane to these olefins has been established (for a preliminary note see *Chem. and Ind.*, 1951, 684). The reactions were carried out in the vapour phase where possible, with light of wave-length >3000 Å, which only the fluoroiodide can absorb. The reactants were carefully purified so that addition reactions catalysed by traces of peroxides present in the olefin, or involving an ionic mechanism, can be excluded; in no instance was a dark reaction observed.

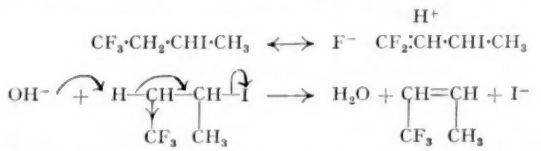
Propylene reacts smoothly with trifluoroiodomethane on exposure to ultra-violet light, and yields only one product, 1 : 1 : 1-trifluoro-3-iodobutane (I) whose identity is proved by its dehydroiodination to 1 : 1 : 1-trifluorobut-2-ene (III), b. p. 20°, and not to the known isomer (IV), b. p. 6·4° (Swarts, *Bull. Soc. chim. Belg.*, 1927, **36**, 191).

CF_3·CH_2·CHI·CH_3 (I)	CF_3·CH:CH·CH_3 (III)	CF_3·CH_2·CH:CH_2 (V)
CF_3·CH(CH_3)·CH_2I (II)	CF_3·C(CH_3):CH_2 (IV)	CF_3·CH_2·CHCl·CH_3 (VI)

Dehydroiodination of (I), which could give (III) or (V), yields only (III), and the absence of (V) (b. p. 10·6°; prepared by two independent routes by Leedham and Steele, unpublished work) is shown by comparison of infra-red spectra. The formation of only (III) affords another example of the marked directing influence of a polyfluoro-group on dehydrohalogenation reactions, caused by the increased acidic character of the α-hydrogen

* Part I, Haszeldine, *J.*, 1952, 2504.

atom by hyperconjugation and inductive effects (cf. Haszeldine, *J.*, 1951, 2495; *Nature*, 1951, **168**, 1028). The infra-red spectrum of (III) (C.S. 1*) shows C–H stretching vibra-



tions at 3·27 μ, and 3·38 and 3·49 μ (doublet), ascribed to the $-CH=$ and CH_3 groups respectively; the strong band at 10·4 μ caused by the carbon–hydrogen out-of-plane bending mode in *trans*-olefins (see Part I), and the C:C stretching vibration at 5·90 μ fully support structure (III). Comparison of the ultra-violet spectra of (III) and its perfluoro-analogue, octafluorobut-2-ene (Haszeldine, *J.*, 1952, 4423), reveals the marked shift to shorter wave-length produced by substitution of hydrogen by fluorine (Table 1).

TABLE 1.

	Extinction coefficients		
mμ:	230	220	210
$CF_3{\cdot}CH{:}CH{\cdot}CH_3$	7·8	17·8	37·8
$CF_3{\cdot}CF{:}CF{\cdot}CF_3$	2·2	4·6	11·6

TABLE 2.

	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
$CF_3{\cdot}CH_2{\cdot}CHClI$ ...	272	430	230	125
$CF_3{\cdot}CH_2{\cdot}CHIF$ ...	260	340	214	46
$CF_3{\cdot}(CH_2{\cdot}CHF)_2{\cdot}I$	258	430	222	100
$CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CH_3$	264	435	220	28

Treatment of (I) with chlorine gave (VI) whose physical properties agreed with those reported for 3-chloro-1 : 1 : 1-trifluorobutane; the isomeric 1-chloro-3 : 3 : 3-trifluoro*iso*-butane derived from (II) is unknown, but would be expected to have an appreciably lower boiling point. Reduction of (I) with zinc and hydrochloric acid yielded 1 : 1 : 1-trifluorobutane, whose b. p. (16·7°) was close to the recorded value (18°).

The above evidence established that the CF_3 radical attacks the terminal methylene group in propylene. The following general mechanism is suggested (R = Me):

Initiation: $CF_3I \longrightarrow CF_3{\cdot} + {\cdot}I$

Propagation: $CF_3{\cdot} + R{\cdot}CH{:}CH_2 \longrightarrow R{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CF_3$

$R{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CF_3 + R{\cdot}CH{:}CH_2 \longrightarrow R{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CHR{\cdot}CH_2{\cdot}CF_3$

Transfer: $R{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CF_3 + CF_3I \longrightarrow R{\cdot}CHI{\cdot}CH_2{\cdot}CF_3 + CF_3{\cdot}$

If it is assumed that the chain-transfer step is equally efficient for the reaction of trifluoroiodomethane with propylene and 3 : 3 : 3-trifluoropropene (see below), then the rates of reaction are $CH_3{\cdot}CH{:}CH_2 > CF_3{\cdot}CH{:}CH_2$. The orientation in radical addition to propylene is in accord with work on the peroxide-catalysed addition of hydrogen bromide, hydrogen sulphide, thiols, bromodichloromethane, and dibromodichloromethane, α-bromoesters, sodium hydrogen sulphite, and sulphuryl chloride (see Hey, *Ann. Reports*, 1944, **41**, 186, and Kharasch *et al.*, 1946—1951, for references). Addition of hydrogen halide under conditions favouring an ionic reaction yields the *iso*propyl derivative and indicates a polarisation $CH_3 \overset{\delta+}{\rightarrow} CH{:}CH_2 \overset{\delta-}{}$.

Irradiation of vinyl chloride and trifluoroiodomethane gives high yields of only one product (VII). As with propylene, only traces of iodine are liberated if the liquid reaction products are shielded from ultra-violet light. The absence of the possible isomer (VIII)

$CF_3{\cdot}CH_2{\cdot}CHClI$	$CF_3{\cdot}CHCl{\cdot}CH_2I$	$CF_3{\cdot}CH{:}CHCl$	$CF_3{\cdot}CCl{:}CH_2$
(VII)	(VIII)	(IX)	(X)

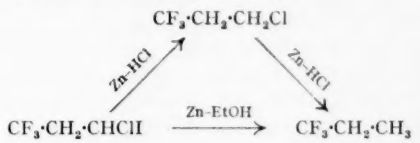
was show by the following reactions: (*a*) Dehydroiodination gave the known 1-chloro-3 : 3 : 3-trifluoropropene (IX), b. p. 21°, and not the known isomer (X), b. p. 14—15° (Haszeldine, *J.*, 1951, 2495). The infra-red spectrum of (IX) (C.S. 2) suggests its formulation as mainly the *trans*-isomer, since olefinic C–H vibrations are apparent at 3·25 and

* Spectra thus designated have been deposited with the Chemical Society (cf. *Proc.*, 1952, 164), and photocopies may be obtained from the General Secretary. The C.S. number must be cited in such requests.

10·70 μ, and the C:C stretching vibration is at 6·06 μ, with a side band at 5·90 μ. (*b*) Treatment of (VII) with chlorine gave the 1 : 1-dichloride (XI), b. p. 72·4°, shown to be different from, and not contaminated by, the 1 : 2-dichloride (XII), b. p. 76·7°, which would have been obtained from (VIII). The infra-red spectra of (XI) (C.S. 3) and (XII) (C.S. 4) (prepared by

(XI) $CF_3{\cdot}CH_2{\cdot}CHCl_2$ $CF_3{\cdot}CHCl{\cdot}CH_2Cl$ (XII)

addition of chlorine to 3 : 3 : 3-trifluoropropene) are readily distinguished by the pattern of the C–F stretching vibrations in the 7·5—9 μ region, and by the presence or absence of the strong band at 10·6 μ (XII), and of the strong bands at 12·95 and 14·6 μ (XI). (*c*) Reaction of the vinyl chloride–trifluoroiodomethane addition product with zinc and ethanol failed to yield the 3 : 3 : 3-trifluoropropene which would be readily obtained from (VIII); instead, reduction of (VII) to 1 : 1 : 1-trifluoropropane was observed. (*d*) Similar reduction was noted on treatment of (VII) with zinc and hydrochloric acid, and under the conditions used 3-chloro-1 : 1 : 1-trifluoropropane was also isolated:



The formation of only 1 : 1 : 1-trifluoropropane (C.S. 5) would not distinguish between (VII) and (VIII), but the intermediate chloro-compound isolated can be derived only from (VII). The chloro-compound is readily distinguished from its isomer ($CF_3{\cdot}CHCl{\cdot}CH_3$, b. p. 30·0°) by its infra-red spectrum (C.S. 6), its b. p. (45°), and by its ready dehydrochlorination to 3 : 3 : 3-trifluoropropene (cf. $CF_3{\cdot}CHCl{\cdot}CH_3$; Haszeldine, *J.*, 1951, 2495).

3-Chloro- and 3-bromo-1 : 1 : 1-trifluoropropane (C.S. 7) are readily prepared from 1 : 1 : 1-trifluoro-3-iodopropane (C.S. 8) by reaction with chlorine or bromine in Pyrex vessels.

The photochemical reaction of trifluoroiodomethane with vinyl chloride in the liquid phase is more rapid than in the vapour phase, but iodine is liberated by photolysis of (VII). A thermal reaction causes substantial decomposition of (VII) to 3-chloro-1 : 1 : 1-trifluoropropane, probably by hydrogen abstraction from a hydrogen-containing molecule, RH:

$$CF_3{\cdot}CH_2{\cdot}CHClI \xrightarrow{\text{Heat}} CF_3{\cdot}CH_2{\cdot}CHCl{\cdot} \xrightarrow{RH} CF_3{\cdot}CH_2{\cdot}CH_2Cl\ (+\ R{\cdot})$$

Hydrogen chloride and polymeric products were also obtained, suggesting that a vinyl chloride polymer $CF_3{\cdot}[CH_2{\cdot}CHCl]_n{\cdot}I$, formed initially, decomposed by dehydrochlorination.

The polarisation of vinyl chloride during reactions involving ionic intermediates can be represented as $\overset{\delta+}{C}HCl{:}\overset{\delta-}{C}H_2$, *e.g.*, in addition of hydrogen chloride, bromide, and iodide, Friedel–Crafts addition of alkyl halides (Schmerling, *J. Amer. Chem. Soc.*, 1946, **68**, 1650; Kharasch *et al.*, *ibid.*, 1934, **56**, 712; *J. Org. Chem.*, 1939, **4**, 429). The direction of addition of the trifluoromethyl radical established above is in accord with the peroxide-catalysed addition of hydrogen bromide to give 1-bromo-2-chloroethane, of hydrogen sulphide to give 2-chloroethanethiol and 2 : 2′-dichlorodiethyl sulphide, of 2-mercaptoethanol to yield 2-chloroethyl 2′-hydroxyethyl sulphide, and of sulphuryl chloride to give 2 : 2-dichloroethanesulphonyl chloride (Vaughan, Rust, and Evans, *loc. cit.*; Fuson and Ziegler, *J. Org. Chem.*, 1946, **11**, 510; Kharasch and Zavist, *loc. cit.*; Yakubovich and Zinov'ev, *loc. cit.*).

Vinyl fluoride reacts with trifluoroiodomethane much faster than does vinyl chloride, and yields (XIII) (C.S. 9) with small amounts of the di-addition product (XV) (C.S. 10).

$CF_3{\cdot}CH_2{\cdot}CHFI$ (XIII) $CF_3{\cdot}CHF{\cdot}CH_2I$ (XIV) $CF_3{\cdot}CH_2{\cdot}CHF{\cdot}CH_2{\cdot}CHFI$ (XV)

That the mono-addition product is (XIII) and not (XIV) is shown by treatment with zinc and dilute acid to give 1 : 1 : 1 : 4-tetrafluoropropane (XVI) (C.S. 11), identical with the

compound obtained by halogen replacement in 1 : 1 : 1-trifluoro-3-iodopropane, or by addition of hydrogen fluoride to 3 : 3 : 3-trifluoropropene :

$$\begin{matrix} CF_3{\cdot}CH_2{\cdot}CHFI \\ CF_3{\cdot}CH_2{\cdot}CH_2I \end{matrix} \xrightarrow[Hg_2F_2]{Zn\text{-}HCl} CF_3{\cdot}CH_2{\cdot}CH_2F \xleftarrow{HF} CF_2{:}CH{\cdot}CH_3$$

(XVI)

Dehydroiodination of (XIII) gave 1 : 3 : 3 : 3-tetrafluoropropene, identical with the compound obtained by addition of hydrogen fluoride to 3 : 3 : 3-trifluoropropyne (Haszeldine, *J.*, 1952, 3490). The infra-red spectrum of the tetrafluoropropene (C.S. 12) shows olefinic C–H absorption at 3·21 and 10·8 μ, and the C:C stretching vibration at 5·90 μ has been moved to lower wave-length relative to that of 1-chloro-3 : 3 : 3-trifluoropropene (see above). The additional band at 5·68 μ may be caused by *cis-trans*-isomerism.

The ultra-violet spectrum of (XV) (Table 2) shows that the alternative formula $CF_3{\cdot}CH_2{\cdot}CHF{\cdot}CHF{\cdot}CH_2I$, containing the CH_2I as distinct from the CHFI chromophore, can be eliminated. This is supported by comparison of the infra-red spectra of (XIII) and (XV), and by the stability of (XV) to water, since compounds with adjacent CHF groups are very unstable and yield CH:CF or C:C by loss of hydrogen fluoride.

Thus addition of the $CF_3{\cdot}CH_2{\cdot}CHF{\cdot}$ radical to a second molecule of vinyl fluoride follows the same orientation as for addition of $CF_3{\cdot}$ to vinyl fluoride. This strongly suggests that polyvinyl fluoride has formula $[{\cdot}CH_2{\cdot}CHF{\cdot}CH_2{\cdot}CHF{\cdot}]$.

Trifluoroiodomethane reacts rapidly with methyl acrylate in the liquid phase to give high yields of the mono-addition compound (XVII), and material of higher boiling point, of general formula (XVIII), partly resolved into its individual members. The direction of

(XVII) $CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CO_2Me$ $\qquad$ $CF_3{\cdot}[CH_2{\cdot}CH(CO_2Me)]_n{\cdot}I$ (XVIII)

addition of the trifluoromethyl radical is established by the conversion of (XVII) (C.S. 13), by zinc and hydrochloric acid, into γγγ-trifluorobutyric acid, identical with material independently synthesised by the sequence :

$$CF_3I + C_2H_4 \xrightarrow{Heat} CF_3{\cdot}CH_2{\cdot}CH_2I \xrightarrow[CO_2]{Mg\text{-}Et_2O;} CF_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

Examination of the infra-red and ultra-violet spectra of the higher-boiling material shows conclusively that it has structure (XVIII). There is a marked similarity in the infra-red spectra of the fractions where in (XVIII) n changes from 1 to 4. The presence of the CO_2Me group is shown by the C:O stretching absorption at 5·75 μ. The ultra-violet spectra (Table 3) show that the C–I chromophore is present, and thus eliminate the possibility that the compound $(CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me)_2$, formed by combination of two resonance-stabilised $CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me$ radicals, is a major reaction product.

TABLE 3.

	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
$CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CO_2Me$	279	390	249	240
$CF_3{\cdot}[CH_2{\cdot}CH(CO_2Me)]_2{\cdot}I$	278	345	251	240
$CF_3{\cdot}[CH_2{\cdot}CH(CO_2Me)]_4{\cdot}I$	270	280	252	253

The addition of hydrogen bromide to acrylic acid yields only one product, β-bromopropionic acid, whether peroxides or antioxidants are added (Walling, Kharasch, and Mayo, *J. Amer. Chem. Soc.*, 1939, **61**, 2693). Thus, it is not known whether the same compound is formed by a reaction involving free radicals as by one involving ionic intermediates, or whether one of the reactions proceeds so much faster than the other that only one product is formed. Studies on the addition of thiols suggest that the $RS{\cdot}$ radical and the RS^- ion become attached to the methylene group in methyl acrylate (Kharasch and Fuchs, *J. Org. Chem.*, 1948, **13**, 97). The present investigation shows quite clearly that free-radical attack takes place on the methylene group.

Results of preparative importance which have emerged during the present work are

the ready conversion, in high yield, of fluoro-iodo-compounds into their fluoro-chloro-, or fluoro-bromo-analogues by reaction with chlorine or bromine on exposure to light of wavelength >3000 Å, and their conversion into the fluoro-hydrogeno-compounds by reaction with zinc in hydrochloric acid or ethanol. These techniques considerably simplify structural determinations. The conversion of >CHI into $>CH_2$ takes place smoothly with zinc and acid or ethanol (*e.g.*, I, XVII), but compounds of the type >CXI can yield >CHX or $>CH_2$. Thus, when X = Cl (VII), only the $>CH_2$ compound is obtained with zinc and ethanol, whereas with zinc and hydrochloric acid equal amounts of the >CHCl and $>CH_2$ compounds are obtained. When X = F (XIII), reaction stops at the >CHF stage, indicating that the CH_2F bond is more stable than the CH_2Cl bond in this type of reaction.

The compound $CF_3{\cdot}CH_2{\cdot}CH_2F$ is the first of the type $R{\cdot}CH_2{\cdot}CH_2F$ (R = polyfluoroalkyl) to be prepared, and it is of interest to ascertain whether the lone C–F bond is appreciably stabilised by the CF_3 group compared with an alkyl fluoride and with the compounds $CF_3{\cdot}CH_2{\cdot}CH_2X$ (X = Cl, Br, I). The marked increase in stability of X in compounds of the type $CF_3{\cdot}CHX{\cdot}CH_3$, with X adjacent to the CF_3 group, relative to those of type $CF_3{\cdot}CH_2{\cdot}CH_2X$ (X = Cl, Br, I), has been noted earlier (Haszeldine, *J.*, 1951, 2495). The increased stability of the CH_2F group relative to the CH_2Cl group indicated above, is not shown to as marked an extent in dehydrohalogenation reactions, since the fluoro- and chloro-compounds both readily yield 3 : 3 : 3-trifluoropropene by reaction with ethanolic potassium hydroxide at room temperature. Thus, for the reaction

$$OH^- + H{-}CH(CF_3){-}CH_2{-}F \longrightarrow H_2O + CF_3{\cdot}CH{:}CH_2 + F^-$$

the acidity of the α-hydrogen atom, increased by the inductive effect of the trifluoromethyl group, and the high solvation energy of the fluoride ion, substantially overcome the expected retardation caused by the difference in the C–F and C–Cl bond energies.

Hydrogen abstraction by the CF_3 radical occurs to a very small extent, and is detected only with propylene, where the resonance stability of the allyl radical becomes important :

$$CF_3{\cdot} + CH_3{\cdot}CH{:}CH_2 \longrightarrow CF_3H + \dot{C}H_2{\cdot}CH{:}CH_2$$

The C–I bond in the addition products containing negative atoms or groups on the same carbon atom, e.g., (VII), (XIII), and particularly (XVII), is susceptible to homolysis, but under optimum conditions no iodine is liberated if the reaction products are shielded from the light, thus showing the efficiency of the chain-transfer step (see mechanism above).

Attack of the CF_3 radical on the olefins $R{\cdot}CH{:}CH_2$ (R = Me, Cl, F, CO_2Me) reported above, and on $R{\cdot}CH{:}CH_2$ (R = CF_3, CN; Haszeldine, Part I, *loc cit.*; *J.*, 1952, 3490), is, within the accuracy of the experiments (*ca.* 5%), *exclusively* on the $:CH_2$ group, and the general mechanism outlined above is suggested. Since in ionic reactions $R{\cdot}CH{:}CH_2$ has a polarisation $R{\cdot}\overset{\delta-}{C}H{:}\overset{\delta+}{C}H_2$ (R = CO_2Me, CF_3, CN) or $R{\cdot}\overset{\delta+}{C}H{:}\overset{\delta-}{C}H_2$ (R = Me, Cl, F), it is evident that the nature of R, and hence the apparent polarisation of the double bond, is of little importance in determining orientation in free-radical attack. This becomes particularly clear by comparison of $CF_3{\cdot}CH{:}CH_2$ and $CH_3{\cdot}CH{:}CH_2$, where the inductive and hyperconjugative (but no mesomeric) effects, which act in the *same* direction and determine the polarisation during ionic attack given above, apparently have no influence in *orientation* in radical attack although they do influence the *rate* of reaction. The situation is more complicated with vinyl chloride and fluoride, where inductive ($X{\leftarrow}CH{:}CH_2$) and back-co-ordination ($\overset{+}{X}{:}CH{\cdot}\overset{-}{C}H_2$) effects act in *opposite* directions, and with acrylonitrile and methyl acrylate, where attack on a conjugated system may be influenced by mesomeric effects. Although the *assumption* that the overall polarisation of the double bond on approach of a neutral CF_3 radical can be inferred from orientation in ionic reactions may well be unjustified, it is unlikely that the direction of radical addition to olefins of such different types should be the same if ionic influences were involved.

If orientation in free-radical addition reactions is governed by the stability of the

intermediate free radical, then it follows that the secondary radicals $CF_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}$, $CF_3{\cdot}CH_2{\cdot}CHCl{\cdot}$, $CF_3{\cdot}CH_2{\cdot}CHF{\cdot}$, $CF_3{\cdot}CH_2{\cdot}CH(CF_3){\cdot}$, $CF_3{\cdot}CH_2{\cdot}CH(CO_2Me){\cdot}$, and $CF_3{\cdot}CH_2{\cdot}CH(CN){\cdot}$ are more stable than the primary radicals $CF_3{\cdot}CH(CH_3){\cdot}CH_2{\cdot}$, $CF_3{\cdot}CHCl{\cdot}CH_2{\cdot}$, $CF_3{\cdot}CHF{\cdot}CH_2{\cdot}$, $(CF_3)_2CH{\cdot}CH_2{\cdot}$, $CF_3{\cdot}CH(CO_2Me){\cdot}CH_2{\cdot}$, and $CF_3{\cdot}CH(CN){\cdot}CH_2{\cdot}$.

It might be argued that steric factors were controlling the orientation in radical addition, but this seems unlikely to cause such great specificity in orientation. Studies in this connection and the factors which affect the stability of free radicals will be discussed in detail in a later communication in this series.

Experimental

Preparation of Materials and General Technique.—Trifluoroiodomethane (*J.*, 1951, 584) was thoroughly washed with 33% aqueous sodium hydroxide and purified by repeated distillation *in vacuo*. Vinyl chloride and fluoride, propene, and methyl acrylate were commercial specimens purified by repeated distillation *in vacuo* or through a packed column in nitrogen, and checked for purity by their infra-red spectra. Extreme precautions were taken to prevent peroxide formation, and once pure the chemicals were manipulated in a vacuum-system.

The reaction vessels were of Pyrex (30- or 300-ml. capacity) or silica (50-ml. capacity), and were placed 10 cm. from a Hanovia ultra-violet lamp used without the Woods filter. The reaction tubes were connected to a vacuum-system by pressure tubing for filling and emptying, and were sealed *in vacuo*. Thermal reactions were carried out in furnaces controlled to ±3°.

Reaction of Trifluoroiodomethane with Propene.—There was no reaction when trifluoroiodomethane (24·7 g., 0·126 mol.) and propene (5·3 g., 0·126 mol.) were sealed in a Pyrex tube and kept in the dark for 14 days. The tube was then exposed to ultra-violet light with the base of the vertical tube shielded to prevent reaction in the liquid phase or photolysis of the reaction products. A slow reaction occurred during 14 days, and fractionation *in vacuo* then gave unchanged reactants (14·6 g., 49%) [Found: *M*, 121. Calc. for $C_3H_6 + ClF_3$ (1 : 1): *M*, 119], liquid products (see below), and a fraction (0·94 g.) which when sealed with bromine (3 ml.) in a Carius tube for 4 days gave propylene dibromide and fluoroform (0·060 g., 1% based on trifluoroiodomethane used) (Found: *M*, 69. Calc. for CHF_3: *M*, 70), identified tensimetrically. The liquid products were shaken with mercury to remove a small amount of iodine and distilled to give 1 : 1 : 1-*trifluoro*-3-*iodobutane* (14·9 g., 98%), b. p. 103·5°/763 mm., n_D^{20} 1·4277 (Found: C, 19·8; H, 2·5%; *M*, 240. $C_4H_6F_3I$ requires C, 20·2; H, 2·5%; *M*, 238). Ultra-violet spectrum: Table 2.

There was no apparent reaction when alcoholic potassium hydroxide (30 ml. of 10%) was slowly added to 1 : 1 : 1-trifluoro-3-iodobutane (1·70 g.), cooled in ice, and stirred for 2 hours. Heating at 80° during 4 hours caused precipitation of potassium iodide, and distillation of the gas evolved and collected in traps cooled by liquid nitrogen gave 1 : 1 : 1-*trifluorobut*-2-*ene* (0·61 g., 77%), b. p. 20° (Found: C, 43·1; H, 4·6%; *M*, 109. $C_4H_5F_3$ requires C, 43·6; H, 4·5%; *M*, 110).

Chlorine (0·55 g.) and 1 : 1 : 1-trifluoro-3-iodobutane (1·68 g.), sealed in a Pyrex tube and exposed to sunlight for 2 hours, then to ultra-violet light for 1 hour, gave, after shaking with mercury to remove iodine and chlorine, 3-chloro-1 : 1 : 1-trifluorobutane (0·97 g., 93%) (Found: C, 32·5; H, 4·2. Calc. for $C_4H_6ClF_3$: C, 32·7; H, 4·1%), b. p. 65·4—66·0°, n_D^{20} 1·3438. Henne and Hinkamp (*J. Amer. Chem. Soc.*, 1945, **67**, 1197) reported b. p. 65·3°, n_D^{20} 1·3433.

To zinc dust (4 g.) and dilute hydrochloric acid (30 ml.) was added 1 : 1 : 1-trifluoro-3-iodobutane (1·37 g.), and the mixture heated under reflux for 4 hours. The volatile products were distilled *in vacuo* to give 1 : 1 : 1-trifluorobutane (0·46 g., 71%) (Found: *M*, 111. Calc. for $C_4H_7F_3$: *M*, 112), b. p. 18°. Henne and Hinkamp (*loc. cit.*) reported b. p. 16·7°.

Interaction of Trifluoroiodomethane and Vinyl Chloride.—(a) *Photochemical, vapour-phase.* Trifluoroiodomethane (25·5 g., 0·13 mol.) and vinyl chloride (8·2 g., 0·13 mol.), sealed in a Pyrex tube, showed no reaction after 15 days in the dark at room temperature. The liquid reactants were then shielded from light, and the vapour phase exposed to ultra-violet light for 14 days. The liquid reaction products, coloured slightly pink by liberated iodine, collected in the shielded portion of the tube. Distillation gave unchanged reactants (16·6 g., 50%) (Found: *M*, 132. Calc. for equimolar amounts of reactants: *M*, 129), and a liquid product, distilled through a small column to give 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane (16·8 g., 97%), b. p. 120°, n_D^{20} 1·453 (Found: C, 14·4; H, 1·3%; *M*, 260. Calc. for $C_3H_3ClIF_3$:

C, 14·0; H, 1·2%; *M*, 258·5). Haszeldine (*J.*, 1951, 2495) reports b. p. 119°, n_D^{20} 1·450. Ultra-violet spectrum: Table 2. Fluoroform was not a product of reaction.

(b) *Photochemical, liquid phase.* Vinyl chloride (2·3 g.) and trifluoroiodomethane (7·0 g.) were sealed in a Pyrex tube, and only the liquid phase was irradiated for 4 days. Much more iodine was liberated than in the vapour-phase reaction, but distillation of the deep red liquid gave 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane (4·4 g., 47%) (identical with that obtained above), unchanged reactants (3·5 g., 38%), and a fraction, b. p. 45—90° (0·80 g.).

(c) *Thermal.* Preliminary experiments in Carius tubes showed that trifluoroiodomethane (2·0 g.) and vinyl chloride (0·6 g.) failed to react below 220° in the dark; at 230° liquid products, iodine, and iodine monochloride were formed, and at 240° copious liberation of iodine was apparent.

Trifluoroiodomethane (37·9 g.) and vinyl chloride (14·8 g.), heated to 230—235° for 4 days in an autoclave (300 ml.), yielded hydrogen chloride (3·5 g., 18% based on vinyl chloride), a mixture of unchanged trifluoroiodomethane (22·4 g., 59%) and vinyl chloride (1·7 g., 11%) (Found: *M*, 187. Calc. for CF_3I: *M*, 196. Calc. for C_2H_3Cl: *M*, 62·5), and the following liquid fractions: (*a*) b. p. 45—50°, n_D^{20} 1·352, 4·5 g.; (*b*) b. p. 50—110°, n_D^{20} 1·409, 3·4 g.; (*c*) 110—120°, n_D^{20} 1·432, 1·3 g. Redistillation of (*a*) gave 3-chloro-1 : 1 : 1-trifluoropropane (Found: C, 27·2; H, 2·8%; *M*, 131. Calc. for $C_3H_4ClF_3$: C, 27·2; H, 3·0%; *M*, 132·5), b. p. 45·8—46·4°/773 mm., n_D^{20} 1·339, identified by comparison of its infra-red spectrum with that of a known specimen, and by the ready dehydrochlorination of a 2·0-g. sample by alcoholic potassium hydroxide (40 ml. of 10%) at 20—40° during 4 hours to give 1 : 1 : 1-trifluoropropene (1·04 g., 72%) (Found: *M*, 96·5. Calc. for $C_3H_3F_3$: *M*, 96). Henne and Whaley (*J. Amer. Chem. Soc.*, 1942, **64**, 1157) report b. p. 45·1°, n_D^{20} 1·3350, for 3-chloro-1 : 1 : 1-trifluoropropane. Infra-red spectroscopic examination of (*c*) showed that it was mainly 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane.

3-Bromo- and 3-chloro-1 : 1 : 1-trifluoropropane are obtained in 80—90% yield by treatment of 1 : 1 : 1-trifluoro-3-iodopropane (1·5 g.) with a slight excess of bromine or chlorine in a Pyrex vessel exposed to ultra-violet light.

(d) *Reactions of 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane.* The compound (1·16 g.) reacted immediately with chlorine (0·353 g.) in a Pyrex tube at room temperature. Iodine monochloride was liberated, and after 12 hours in the dark was removed with the excess of chlorine by shaking the whole with mercury. Distillation gave 3 : 3-dichloro-1 : 1 : 1-trifluoropropane (0·59 g., 80%), b. p. 72·8—73·4°/766 mm., n_D^{20} 1·363 (Found: C, 21·3; H, 1·8%; *M*, 166. Calc. for $C_3H_3Cl_2F_3$: C, 21·6; H, 1·8%; *M*, 167). Henne and Whaley (*loc. cit.*) report b. p. 72·4°, n_D^{20} 1·3631.

For comparison, 2 : 3-dichloro-1 : 1 : 1-trifluoropropane (1·45 g., 83%) b. p. 76·6—77·2°, n_D^{20} 1·367, was prepared by addition of chlorine (0·75 g.) to 1 : 1 : 1-trifluoropropene (1·0 g.; prepared by dehydroiodination of 1 : 1 : 1-trifluoro-3-iodopropane). Henne and Whaley (*loc. cit.*) report b. p. 76·7°, n_D^{20} 1·3671.

To ice-cold 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane (1·8 g.) was added 10% ethanolic potassium hydroxide (40 ml.), potassium iodide being precipitated. After 2 hours the mixture was acidified (dilute hydrochloric acid), then a large excess of water was added. The volatile products were transferred to a vacuum-system and distilled, to give 1-chloro-3 : 3 : 3-trifluoropropene (0·74 g., 82%), b. p. 20·8° (Found: *M*, 129·5. Calc. for $C_3H_2ClF_3$: *M*, 130·5). Haszeldine (*loc. cit.*) reports b. p. 21°.

Reduction of 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane (1·3 g.) with zinc dust (4 g.) and dilute hydrochloric acid (25 ml.) at *ca.* 80° for 4 hours gave, as products carried through a reflux condenser into a liquid air trap: (*a*) 3-chloro-1 : 1 : 1-trifluoropropane (0·225 g., 34%) and 1 : 1 : 1-trifluoropropane (0·065 g., 13%) as a mixture (*M*, 125) which could not be separated by distillation, but which infra-red spectroscopic examination showed to contain only the two components (*M*, 132·5 and 98 respectively); (*b*) 1 : 1 : 1-trifluoropropane (0·105 g., 21%) (Found: *M*, 98·5), b. p. −13°. The total yield of 1 : 1 : 1-trifluoropropane is thus 34%. Attempts to bring about a reduction to only 3-chloro-1 : 1 : 1-trifluoropropane failed.

Treatment of 3-chloro-1 : 1 : 1-trifluoro-3-iodopropane (1·14 g.) with zinc (4 g.) and refluxing ethanol (30 ml.) for 6 hours, followed by addition of an excess of water to the flask and fractionation of the combined volatile products *in vacuo*, gave 1 : 1 : 1-trifluoropropane (0·22 g., 51%) and no 3 : 3 : 3-trifluoropropene.

Interaction of Trifluoroiodomethane and Vinyl Fluoride.—Vinyl fluoride (4·07 g.) and trifluoroiodomethane (17·4 g.) were sealed in a Pyrex vessel and the vapour phase was irradiated for 14 days. The unchanged reactants (5·0 g., 23%) (Found: *M*, 120. Calc. for equimolar

mixture of CF_3I and C_2H_3F : *M*, 121) were separated in a vacuum-system from the colourless liquid products, distillation of which gave **1 : 1 : 1 : 3-*tetrafluoro-3-iodopropane*** (13·9 g., 84%), b. p. 86·2°/757 mm., n_D^{20} 1·4024 (Found : C, 14·7; H, 1·5%; *M*, 240. $C_3H_3F_4I$ requires C, 14·9; H, 1·2%; *M*, 242), and **1 : 1 : 1 : 3 : 5-*pentafluoro-5-iodopentane*** (1·5 g., 7%), b. p. 64°/20 mm., n_D^{20} 1·421 (Found : C, 20·2; H, 2·0. $C_5H_6F_5I$ requires C, 20·8; H, 2·0%).

Reduction of **1 : 1 : 1 : 3**-tetrafluoro-3-iodopropane (1·9 g.) at 70° for 4 hours with zinc dust (4 g.) and dilute hydrochloric acid (30 ml.) gave as volatile product **1 : 1 : 1 : 3-*tetrafluoropropane*** (0·72 g., 79%), b. p. 29·4°/761 mm., 23·0°/590 mm. (Found : C, 31·3; H, 3·4%; *M*, 116·5. $C_3H_4F_4$ requires C, 31·0; H, 3·4%; *M*, 116).

Ethanolic potassium hydroxide (15 ml. of 10%), slowly added to **1 : 1 : 1 : 3**-tetrafluoro-3-iodopropane (2·5 g.), caused only a slight precipitation of potassium iodide at room temperature. After 4 hours' heating at 60°, an excess of water was added, and the combined volatile products, which had passed through a reflux water condenser and collected in liquid oxygen-cooled traps, were distilled *in vacuo*, to give **1 : 3 : 3 : 3-*tetrafluoropropene*** (0·94 g., 80%), b. p. −16° (Found : C, 31·3; H, 1·9%; *M*, 115. $C_3H_2F_4$ requires C, 31·6; H, 1·8%; *M*, 114).

Alternative Synthesis of **1 : 1 : 1 : 3-*Tetrafluoropropane***.—To mercurous fluoride (5·0 g.), thoroughly dried in a platinum dish at 110°, in a 10-ml. Pyrex flask, was added **1 : 1 : 1**-trifluoro-3-iodopropane (2·0 g.) (Haszeldine, *J.*, 1949, 2856), and the mixture was heated at 120° under reflux for 5 hours. The volatile products were distilled to give **1 : 1 : 1 : 3**-tetrafluoropropane (0·42 g., 41%), b. p. 29° (Found : *M*, 116. Calc. for $C_3H_4F_4$: *M*, 116), shown to be identical with the material obtained above by comparison of their infra-red spectra.

Dehydrofluorination of **1 : 1 : 1 : 3-*Tetrafluoropropane***.—The compound (0·280 g.) shaken with 10% ethanolic potassium hydroxide (3 ml.) in a sealed tube at 20° for 24 hours gave **3 : 3 : 3**-trifluoropropene (0·219 g., 94%) (Found : *M*, 96. Calc. for $C_3H_3F_3$: *M*, 96), identified tensimetrically.

Interaction of Trifluoroiodomethane and Methyl Acrylate.—No dark reaction was detected. Methyl acrylate (2·0 g., 0·023 mol.) and trifluoroiodomethane (7·2 g., 0·036 mol.) were sealed in a Pyrex tube and irradiated for 4 days at a distance of 8 cm. from the ultra-violet source. Under these conditions, with most of the trifluoroiodomethane present in the liquid phase, the time of irradiation is critical, and if prolonged, breakdown of the products occurs. Distillation gave unchanged trifluoroiodomethane (5·2 g., 72%), methyl acrylate (1·0 g., 50%), and ***methyl γγγ-trifluoro-α-iodobutyrate*** (2·6 g., 88%), b. p. 82°/42 mm., n_D^{20} 1·440 (Found : C, 21·5; H, 2·3. $C_5H_6O_2F_3I$ requires C, 21·3; H, 2·1%). The iodo-ester readily liberates iodine on exposure to light and is preferably distilled at >110° in nitrogen.

In a second experiment, methyl acrylate (8·38 g., 0·098 mol.) and trifluoroiodomethane (17·9 g., 0·091 mol.) were irradiated in a Pyrex vessel for 6 days, to give methyl γγγ-trifluoro-α-iodobutyrate and 6 g. of a polymer distilled through a Vigreux column : (*a*) b. p. 112°/3 mm., n_D^{20} 1·447 (Found : C, 31·5; H, 3·1%), and (*b*) b. p. 138° ± 2°/0·1 mm., n_D^{20} 1·443 (Found : C, 39·0; H, 4·2%). Compounds of general formula $CF_3{\cdot}[CH_2{\cdot}CH(CO_2Me)]_n{\cdot}I$ have analysis : $n = 1$, C 21·3, H 2·1; $n = 2$, C 29·4, H 3·3; $n = 3$, C 34·4, H 4·0; $n = 4$, C 37·8, H 4·4%. Calc. for $[CF_3{\cdot}CH_2{\cdot}CH(CO_2Me)]_2$: C, 38·7; H, 3·9%.

Methyl γγγ-trifluoro-α-iodobutyrate (0·65 g.) was heated under reflux with zinc dust (2 g.) and 50% sulphuric acid until the zinc dissolved. Ether extraction followed by drying ($MgSO_4$) and distillation gave γγγ-trifluorobutyric acid (0·32 g., 48%), b. p. 70°/12 mm., which crystallised. Comparison of its infra-red spectrum with that of a genuine specimen confirmed its identity.

Ultra-violet Absorption Spectra.—A Beckman DU and a Unicam instrument were used to obtain the data shown in Table 1 (vapours), and Tables 2 and 3 (ethanolic solutions).

Grateful acknowledgment is made to Imperial Chemical Industries Limited, for a sample of vinyl chloride and to Dupont Ltd., for a gift of vinyl fluoride. One of the authors (B. R. S.) is indebted to the D.S.I.R. for a maintenance grant.

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242. *Infra-red Spectroscopy and Structural Chemistry. Part IV.* The Infra-red Spectra of Some Tetronic Acids.*

By L. A. Duncanson.

The infra-red spectra have been measured of some tetronic acids as solids and as solutions in various solvents. In some cases it has been found that the keto-forms of the acids predominate in solution.

The production of tetronic acid derivatives (*i.e.*, lactones of γ-hydroxy-β-keto-acids, I) by micro-organisms (Raistrick, *Proc. Roy. Soc.*, 1950, **136**, *B*, 481) and the biological interest concerning them made it desirable that the infra-red spectra of some simple tetronic acids should be investigated more fully than hitherto. During this work it has become apparent that infra-red spectra can provide a useful means of identification for this type of compound. The vibrational spectra of some substances related to tetronic acid (II; R = R′ = R″ = H) have been described by Trotter, Thompson, and Wokes (*Biochem. J.*, 1948, **42**, 601), whose studies included the infra-red spectra of hydroxytetronic acid and ascorbic acid, and by Edsall and Sagall (*J. Amer. Chem. Soc.*, 1943, **65**, 1312), who measured the Raman spectra of tetronic acid, nitrotetronic acid, ascorbic acid, and their sodium salts in aqueous solutions. The ultra-violet absorption spectra of some tetronic

acids have been described by Herbert and Hirst (*Biochem. J.*, 1935, **29**, 1881) and by Jones and Whiting (*J.*, 1949, 1419) who concluded that, in alcoholic solutions, tetronic acids exist in the enol form (II). A similar conclusion for dioxan solutions was reached by Kumler (*J. Amer. Chem. Soc.*, 1940, **62**, 3292) by means of dipole-moment measurements. The work now described includes a study of the infra-red spectra of some tetronic acids in solution and this provides evidence that in some solvents an equilibrium between the ketonic and the enolic forms (I and II) can exist, with the keto-form predominating.

Experimental

M. p.s are corrected. Microanalyses are by Mr. W. Brown.

The tetronic acids were prepared by known methods. They were carefully purified to constant m. p. before use, and found to be analytically pure.

Tetronic acid was prepared by Wolffe and Schwabe's method (*Annalen*, 1896, **292**, 231) except that the intermediate bromotetronic acid was reduced catalytically (palladium–charcoal) instead of with sodium amalgam. Purified by sublimation *in vacuo*, it had m. p. 139—140°. α-Acetyltetronic acid was prepared as described by Benary (*Ber.*, 1909, **42**, 3912), the isolation of the product being modified slightly as follows. The alkaline solution remaining after the hydrolysis of the α-acetyltetronic acid amide was treated with chloroform and then acidified with 6N-nitric acid while the mixture was shaken. Crude α-acetyltetronic acid was obtained as a yellowish solid from the chloroform layer and was purified by sublimation *in vacuo* and crystallisation from benzene, then having m. p. 80—81°. α-Ethyl- and (±)-γ-methyl-tetronic acids, prepared according to Clutterbuck, Raistrick, and Reuter's method (*Biochem. J.*, 1935, **29**, 316, 1308), had m. p. 126° and 118°, respectively.

Samples of the lactone of β-hydroxy-β-1-hydroxy*cyclo*hexylacrylic acid and its methyl ether were kindly provided by Professor E. R. H. Jones, F.R.S., and samples of terrestric and carolic acids by Professor H. Raistrick, F.R.S.

Infra-red measurements were made with a modified Hilger D 209 spectrometer (Grove and Willis, *J.*, 1951, 877). Solid samples were finely ground and suspended in "Nujol" between rock-salt plates in the usual way. Ultra-violet absorption was measured with a Unicam S.P. 500 spectrophotometer.

Solvents were dried and distilled before use. The chloroform used contained about 1% of ethyl alcohol as a stabiliser and no precautions were taken to remove it.

* Part III, *J.*, 1952, 3345.

Results and Discussion

It is proposed to limit the discussion principally to the 5·0—6·5 μ region of the spectra, wherein double-bond stretching modes usually produce well-marked absorption bands. At longer wave-lengths it is difficult to assign bands to particular vibrational modes of complex molecules and at shorter wave-lengths the poor resolving power of the rock-salt prism makes accurate observations difficult. The 5·0—6·5 μ region is adequate for the purpose of discussing the structure of tetronic acids and, in conjunction with the spectra of the solids between 3 and 4 μ, seems to provide a useful means of determining in many cases whether a substance is a tetronic acid or not.

In Table 1 are listed the frequencies of the absorption maxima observed for the different

TABLE 1. *Frequencies of double-bond stretching bands of some tetronic acids in the solid state and in solution.*

Compound	Solid	$CHCl_3$ + 1% EtOH	Solvents $C_2H_4Cl_2$	CCl_4
Tetronic acid: R = R′ = R″ = H	OH {2620 {2530 1690 s 1636 m 1565 s	~1820 w 1778 * 1738 s 1632 s (0·03; 0·25 mm.)	—	—
α-Ethyltetronic acid: R = Et, R′ = R″ = H	OH 2690 1720 m 1650 s 1580 *	1744 s 1675 s (0·051; 0·25 mm.)	3470 w 1760 s 1675 s (0·021; 0·25 mm.) (0·00116; 5·5 mm.)	1818 m. 1771 s 1731m 1672 s (Sat.; 10·5 mm.)
γ-Methyltetronic acid: R′ = Me, R = R″ = H	OH {2640 {2540 1720 s 1634 m 1575 s	~1810 w 1758 m 1739 s 1632 s (0·039; 0·25 mm.)	1811 m 1762 s 1640 w (0·028; 0·25 mm.)	1811 m 1765 s (Sat.; 10·5 mm.)
β-Hydroxy-β-1-hydroxy*cyclo*-hexylacrylic lactone: R′R″ = $[CH_2]_5$>, R = H	OH {2695 {2510 1683 s 1565 s	~1790 w 1746 s 1630 s (0·03; 0·25 mm.)	1793 m 1757 s ~1680 w ~1620 w (0·018; 0·25 mm.)	—
α-Acetyltetronic acid: R = Ac, R′ = R″ = H	OH 3080 1758 s 1675 s 1600 s	1772 s 1705 s 1675 m 1610 s (0·031; 0·25 mm.)	1772 s 1700 s 1673 m 1615 s (0·021; 0·25 mm.)	1784 s 1706 s 1676 m 1617 s (0·035; 0·25 mm.) (0·0011; 5·5 mm.)

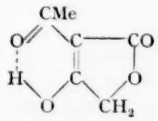
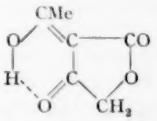
Intensities denoted by: s = strong; m = medium; w = weak.
Molar concentrations and cell lengths given in parentheses.

* Shoulder.

tetronic acids as solids and in solutions. The Figure shows a few of the spectra in order that the general pattern of the changes produced by different solvents can be visualised.

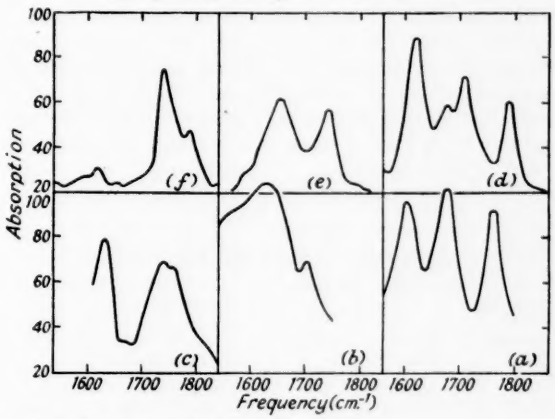
It is seen that, with the exception of α-acetyltetronic acid, all the acids have much lower-frequency carbonyl bands in the solid state than would normally be expected for five-membered-ring lactones (see Grove and Willis, *loc. cit.*). This is interpreted to mean that strong intermolecular association through hydrogen bonds occurs in the solids. In this respect, tetronic acid and the alkyltetronic acids studied show a strong resemblance to the enolised six-membered-ring 1 : 3-diketones such as dimedone (Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068) and this similarity is further emphasised by the relatively low frequencies of their OH stretching bands (2530—2650 $cm.^{-1}$) in the solid state. The spectrum of α-acetyltetronic acid has a band at 1758 $cm.^{-1}$ which is assigned to the lactone-carbonyl group. It is apparent that in this case the lactone-carbonyl group does not take part in hydrogen-bond formation in the solid state. Bands at 3080, 1675, and 1600 $cm.^{-1}$ are assigned respectively to vibrations involving OH stretching, >C=O stretching, and C=C stretching in the system ·C(OH):C·C:O which forms part of structures (III) and (IV). An analogy can again be found in the case of the enolised 1 : 3-diketones by comparing the carbonyl absorption of dimedone

(1605 cm.$^{-1}$; Rasmussen *et al.*, *loc. cit.*) with the corresponding band in its 2-acetyl derivative (1670 cm.$^{-1}$) reported by Birch (*J.*, 1951, 3026). In this case, as with the tetronic acids, the acetyl-carbonyl group presumably forms an intramolecular hydrogen bond with the enolic hydroxyl group, thereby leaving the remaining carbonyl free from intermolecular bonding.

(III)   (IV)

Before leaving the subject of the spectra in the solid state, it must be pointed out that the assignment of bands to specific groups is complicated in many cases by the appearance of more bands in the double-bond stretching region than there are double bonds in the molecules concerned. There are various possible explanations of this anomaly which are however, outside the scope of this paper.

Absorption spectra of some tetronic acids.



(*a*) α-Acetyltetronic acid (solid).
(*b*) α-Ethyltetronic acid (solid).
(*c*) γ-Methyltetronic acid in $CHCl_3$ (0·039M; 0·25-mm. cell).
(*d*) α-Acetyltetronic acid in CCl_4 (0·025M; 0·25-mm. cell).
(*e*) α-Ethyltetronic acid in $CH_2Cl{\cdot}CH_2Cl$ (0·22M; 0·25-mm. cell).
(*f*) γ-Methyltetronic acid in $CH_2Cl{\cdot}CH_2Cl$ (0·028M; 0·25-mm. cell).

The effect of dissolving tetronic acid and the alkyltetronic acids in chloroform is to shift the bands assigned to double-bond stretching modes to higher frequencies, thereby confirming that the compounds are associated by intermolecular hydrogen bonds in the solid state. The frequencies occurring in the chloroform solutions are consistent with the acids being lactones of γ-hydroxy-β-keto-carboxylic acids in the enolic form (II). Thus the strong bands occurring in all the spectra at 1740—1750 cm.$^{-1}$ are due to the $\Delta^{\alpha\beta}$-five-ring lactone-carbonyl groups, and those near 1630 cm.$^{-1}$ to the C=C stretching modes. The effect of an alkyl substituent on this double-bond frequency, *e.g.*, in the case of α-ethyltetronic acid, is to raise it to 1675 cm.$^{-1}$. Under similar conditions α-acetyltetronic acid shows a less marked change in its lactone-carbonyl band compared with that in the solid, which confirms that intermolecular bonding does not take place in the crystalline state of this compound. The spectra of solutions of α-acetyltetronic acid all have the strong band which occurs for the solid at 1675 cm.$^{-1}$ replaced by a strong band near 1700 cm.$^{-1}$ together with a somewhat weaker one near 1675 cm.$^{-1}$. This may mean that in solution the acid exists as an equilibrium mixture of (III) and (IV), the ketonic carbonyl groups in the two cases having different frequencies owing to their different situations in the molecule.

In the spectra of tetronic and the γ-substituted tetronic acids in chloroform solution it

can be seen that weak bands occur at frequencies higher than 1750 cm.$^{-1}$ and this suggests that a keto–enol equilibrium is present with the enol predominating. This equilibrium can be altered by changing the solvent, a suitable one being ethylene dichloride. This solvent absorbs in the region 1650—1800 cm.$^{-1}$ which makes it unsuitable for use with very dilute solutions in thick cells, but for cell thicknesses up to 0·25 mm. it is quite satisfactory and only tetronic acid itself is too insoluble for useful observations to be made. With the other acids in this solvent some interesting results were obtained. γ-Methyltetronic acid and the lactone of β-hydroxy-β-1-hydroxy*cyclo*hexylacrylic acid both show well-marked absorption bands near 1800 and 1760 cm.$^{-1}$, which are the frequencies expected for saturated 5-ring lactone and saturated 5-ring ketone carbonyl groups respectively. Hence it must be presumed that in ethylene dichloride the keto-forms of these acids predominate (I; R = R′ = H, R″ = Me; I; R = H, R′R″ = $[CH_2]_5$ >). This is confirmed by the almost complete disappearance of the band due to the C=C stretching modes near 1630 cm.$^{-1}$. α-Ethyltetronic acid, on the other hand, gives no indication of the presence of the keto-form and it must be concluded that the α-alkyl substituent stabilises the enol form. This stabilisation may be due, at least in part, to hyperconjugation. The spectrum of α-acetyltetronic acid in ethylene dichloride shows no appreciable differences from that in chloroform, again demonstrating the insensitivity of this molecule to changes in environment.

By using a 10-mm. cell it was also possible to measure the absorption spectra of saturated solutions of α-ethyl- and γ-methyl-tetronic acids in carbon tetrachloride. The latter acid again showed bands corresponding to the keto-form, while bands in the spectrum of α-ethyltetronic acid at 1818, 1770, 1731, and 1672 cm.$^{-1}$ indicate the presence of a keto–enol mixture. In neither of these carbon tetrachloride solutions could OH absorption be found, but better resolution might make such an observation possible in the case of α-ethyltetronic acid.

TABLE 2. *Ultra-violet absorption.*

Compound	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	Compound	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
α-Ethyltetronic acid (concn. in $C_2H_4Cl_2$, 8·28 × 10^{-4}M):			γ-Methyltetronic acid (concn. in $C_2H_4Cl_2$, 11·1 × 10^{-4}M):		
(i) In ethylene dichloride	225	4·0	(i) In ethylene dichloride	~219	2·9
(ii) In aqueous H_2SO_4	233	4·1	(ii) In aqueous H_2SO_4	226—227	4·2

Cell length, 0·1 cm. The values for solutions in dilute mineral acid are taken from Herbert and Hirst (*loc. cit.*).

Some ultra-violet absorption measurements were made on solutions in ethylene dichloride of α-ethyl- and γ-methyl-tetronic acids, which confirm the conclusions drawn from the infra-red spectra. It was found that 0·1 cm. of the solvent only transmitted about 3% of the incident light at 220 mμ, but by using very wide slits (2 mm.) it was just possible to make measurements in this region. They are presented in Table 2, together with the corresponding results of Herbert and Hirst (*loc. cit.*) for the undissociated molecules in aqueous solution. The figures show that α-ethyltetronic acid absorbs strongly near 225 mμ in ethylene dichloride and at 233 mμ in aqueous solution, while γ-methyltetronic acid absorbs much more weakly in this region when dissolved in ethylene dichloride. This indicates that in both ethylene dichloride and dilute aqueous mineral acid α-ethyltetronic acid exists as the enol form, but that the enol form of γ-methyltetronic acid is not present to any great extent in ethylene dichloride solution.

It can now be seen how infra-red spectroscopy may be used to identify tetronic acids and, in some cases, to draw conclusions about the positions of substituent groups. It must be emphasised, however, that these results have been obtained from a study of only five compounds and it is possible that other tetronic acids might behave differently. This being borne in mind, the infra-red absorption of tetronic acids can be summarised as follows: (i) In the solid state, alkyltetronic acids have strong hydroxyl absorption bands in the range 2500—2700 cm.$^{-1}$ and strong double-bond stretching bands near 1650—1700 cm.$^{-1}$ and 1565—1580 cm.$^{-1}$, due to the enol forms associated through strong intermolecular hydrogen bonds. (ii) Dilute solutions of alkyltetronic acids in chloroform containing a trace of alcohol show bands near 1740 and 1630 cm.$^{-1}$ (1740 and 1675 cm.$^{-1}$

for α-substituted acids) corresponding to the monomeric enol forms. (iii) γ-Alkyltetronic acids dissolved in ethylene dichloride have absorption bands near 1800 and 1760 cm.$^{-1}$, which correspond to the keto-forms. (iv) α-Acyltetronic acids do not show a marked change in the general pattern of their absorption spectra in passing from the solid state to solution. The last generalisation presumably applies to all tetronic acids in which the enolic OH group is able to form an intramolecular hydrogen bond with an oxygen atom. This class includes ascorbic and hydroxytetronic acids, which were found by Trotter *et al.* (*loc. cit.*) to have absorption maxima at 1750 cm.$^{-1}$ (lactone >C=O) and 1650 cm.$^{-1}$ (C=C) in the solid state.

The spectra of terrestric and carolic acids, two naturally occurring compounds related to tetronic acid, have been measured and they are consistent with the structures proposed for the acids by Raistrick *et al.* (*Biochem. J.*, 1935, **29**, 871; 1936, **30**, 2194). The spectra of the solids include strong bands near 1745, 1710, and 1610 cm.$^{-1}$ which are assigned to the tetronic acid (lactone) >C=O group, the side-chain aliphatic ketone group, and the carbon–carbon double bond, respectively. Under anhydrous conditions these compounds are more closely related to the alkyl ethers of tetronic acids than to the acids themselves, and, for comparison, the spectrum of the methyl ether of β-hydroxy-β-1-hydroxycyclohexylacrylic acid was measured in the solid state. It had strong bands at 1735 and 1628 cm.$^{-1}$ corresponding to those near 1745 and 1610 cm.$^{-1}$ in the spectra of terrestric and carolic acids. The spectra of the acids dissolved in chloroform are similar to those of the solids, there being strong bands in the double-bond stretching region near 1760, 1710, and 1610 cm.$^{-1}$. Neither of these compounds shows OH absorption near 3 μ, which is also in agreement with the proposed structures.

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243. *Elimination Reactions of Esters. Part I. The Formation of αβ-Unsaturated Acids from β-Acyloxy-compounds.*

By R. P. Linstead, L. N. Owen, and R. F. Webb.

The action of alkali on β-acyloxy-esters >C(OY)·CH_2·CO_2R, under conditions when the parent β-hydroxy-compounds (Y = H) are not dehydrated, gives the unsaturated product >C:CH·CO_2H when Y = Ac, COPh, PO_3H_2, $PO(OPh)_2$, NO_2, SO_2Me, or SO_2·C_6H_4Me-*p*, the proportion of elimination to hydrolysis (at the β-carbon atom) increasing with the strength of the acid YOH. The proportion of elimination is also greater when the resulting unsaturated acid is highly conjugated.

This series of papers is concerned with a novel reaction of certain esters, which can be represented by the general scheme :

$$YO{\cdot}CRR'{\cdot}CHR''{\cdot}X + OH^- \longrightarrow CRR':CR''{\cdot}X + YO^- + H_2O$$

where X = an electron-attracting group, such as carbalkoxyl, and Y = an acyl group, such as R·CO, or R·SO_2. Thus, when β-hydroxy-esters and similar compounds are acylated and subsequently treated with alkali, the normal hydrolysis of the acyl group (Y) may be either partly or wholly superseded by elimination, with the formation of an αβ-double bond. The present paper is concerned with the simple cases in which R, R', and R'' are all hydrogen, alkyl, or aryl. As the general reaction has not previously been examined we have begun with a survey of its scope and potentialities and have not as yet studied the mechanism in detail.

The reaction is related to the formation of αβ-unsaturated products by the action of

bases on the corresponding β-halides. Whilst there are many examples of this, the observed eliminations of β-acyloxy-groups are few and scattered. Blaise and Maire (*Ann. Chim. Phys.*, 1908, **15**, 556) found that the ketone (I) on treatment with hot aqueous alkali gave the unsaturated compound (II). Schmidt and Rutz (*Ber.*, 1928, **61**, 2142) converted a series of β-acetyloxynitro-compounds (III) into the nitro-olefins (IV) by reaction with potassium hydrogen carbonate in ether. In applying the latter reaction to carbohydrate chemistry, Fischer and Sowden (*J. Amer. Chem. Soc.*, 1947, **69**, 1048) showed

$$\underset{\text{(I)}}{CH_3{\cdot}CH(OAc){\cdot}CHEt{\cdot}COEt} \longrightarrow \underset{\text{(II)}}{CH_3{\cdot}C{:}CEt{\cdot}COEt} \qquad \underset{\text{(III)}}{R{\cdot}CH(OAc){\cdot}CH_2{\cdot}NO_2} \longrightarrow \underset{\text{(IV)}}{R{\cdot}CH{:}CH{\cdot}NO_2}$$

$$\underset{\text{(V)}}{AcO{\cdot}CH_2{\cdot}[CH(OAc)]_4{\cdot}CH_2{\cdot}NO_2} \longrightarrow \underset{\text{(VI)}}{AcO{\cdot}CH_2{\cdot}[CH(OAc)]_3{\cdot}CH{:}CH{\cdot}NO_2}$$

that only β-acetoxy-groups were eliminated; thus (V) gave (VI). The isomerisation of certain lactones to unsaturated compounds by bases is a related process, first observed by Beschke (*Annalen*, 1911, **384**, 143) and by Pauly and Will (*ibid.*, 1918, **416**, 1) and since studied in detail by Elvidge, Linstead, Sims, and others (*J.*, 1950, 2228, 2235; 1951, 3386; 1952, 1026).

In our experimental work three structural features have been modified. The electron-attracting groups X used were ester and carboxylic acid; the carbon skeletons were butyric, β-phenylpropionic, δ-phenylvaleric, and *cyclo*hexylacetic; and the acyl groups Y were acetyl, benzoyl, methanesulphonyl, toluene-*p*-sulphonyl, nitro-, phosphonyl, and diphenylphosphonyl. The results are summarised in the Table and special features of interest are discussed in the subsequent paragraphs.

The Alkaline Hydrolysis of β-Acyloxy-esters.

No.	Compound	Alkali	Solvent	Time (hr.)	Temp.	Unsaturated acid formed (%)	Unsaturated acid isolated (%)
(VII)	$Me{\cdot}CH(OAc){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*a*	8	Reflux	54	30
		0·8N-NaOH	*a*	4	,,	44	30
	$Me{\cdot}CH(OBz){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*a*	8	,,	73	35
		0·8N-NaOH	*a*	4	,,	60	40
	$Me{\cdot}CH(OMs){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*a*	8	,,	85	63
		0·8N-NaOH	*a*	2	,,	98	68
(X)	$Me{\cdot}CH(OTs){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*a*	8	,,	79	61
		0·8N-NaOH	*a*	2	,,	96	65
(XI)	$Me{\cdot}CH(O{\cdot}NO_2){\cdot}CH_2{\cdot}CO_2Me$	N-KOH	*a*	,,	,,	—	80
(XII)	$Me{\cdot}CH(O{\cdot}PO_3Ph_2){\cdot}CH_2{\cdot}CO_2Et$	N-KOH	*a*	,,	,,	—	75
(XIII)	$Me{\cdot}CH(O{\cdot}PO_3H_2){\cdot}CH_2{\cdot}CO_2Et$ ...	N-KOH	*a*	,,	,,	—	33
(XIV)	$C_6H_{10}(OAc){\cdot}CH_2{\cdot}CO_2Et$	0·25N-Na_2CO_3	*d*	28	,,	—	23
		0·1N-KOH	*b*	160	R.t.	—	26
		0·5N-KOH	*b*	48	,,	—	24
		0·1N-NaOEt	*e*	17	Reflux	—	23 *
(XVII)	$Ph{\cdot}CH(OAc){\cdot}CH_2{\cdot}CO_2H$	N-Na_2CO_3	*d*	2	90°	—	11
		N-NaOH	*d*	20	R.t.	—	14
		0·1N-KOH	*b*	2	Reflux	—	0
		0·1N-$Ba(OH)_2$	*d*	,,	90°	—	0
(XVIII)	$Ph{\cdot}CH(OAc){\cdot}CH_2{\cdot}CO_2Me$	N-Na_2CO_3	*d*	2·5	,,	—	49
		N-NaOH	*b*	48	R.t.	—	54
		0·1N-KOH	*b*	2·5	Reflux	—	55
		0·1N-$Ba(OH)_2$	*b*	,,	,,	—	0
(XXI)	$Ph{\cdot}[CH_2]_2{\cdot}CH(OAc){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*c*	48	R.t.	14	—
		0·5N-Na_2CO_3	*c*	8	Reflux	22	—
		0·1N-KOH	*c*	,,	,,	19	—
		0·2N-KOH	*c*	48	R.t.	15	12
(XXI)	$Ph{\cdot}[CH_2]_2{\cdot}CH(OBz){\cdot}CH_2{\cdot}CO_2Et$	N-Na_2CO_3	*c*	,,	,,	33	—
		0·5N-Na_2CO_3	*c*	8	Reflux	34	—
		0·1N-KOH	*c*	,,	,,	29	—
		0·2N-KOH	*c*	48	R.t.	24	—

Solvents: (*a*) 1 : 1 Aq. dioxan; (*b*) 1 : 1 aq. MeOH; (*c*) 1 : 1 aq. EtOH; (*d*) H_2O; (*e*) EtOH.
* Partly as ethyl ester.
R.t. = room temperature.
Ms = methanesulphonyl; Ts = toluene-*p*-sulphonyl.

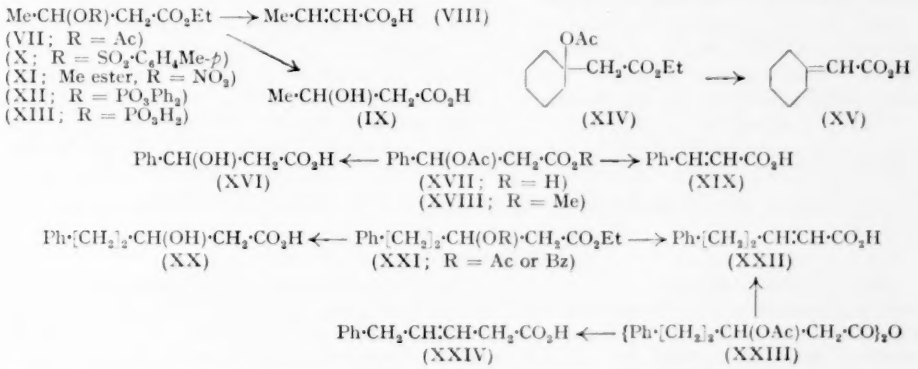
When ethyl β-acetoxybutyrate (VII) was treated with the alkaline solutions mentioned in the Table, in boiling aqueous dioxan, a mixture of crotonic (VIII) and β-hydroxybutyric

acid (IX) was found. The crotonic acid was easily isolated by preferential extraction of the hydroxy-acid with water. For quantitative purposes the yield was estimated by bromine addition to an aliquot portion of the reaction mixture. Control experiments showed that ethyl β-hydroxybutyrate was not dehydrated even with higher concentrations of alkali, and the unsaturated acid is therefore formed by an elimination reaction involving the acetoxy-group. Similar results were obtained with ethyl β-benzoyloxybutyrate, the yield of unsaturated acid then being much greater.

Since sulphonic esters, even when not activated by electron-attracting groups, show a readiness to undergo elimination reactions, particularly when they are derivatives of secondary alcohols (see, *inter al.*, Clarke and Owen, *J.*, **1950**, 2103), higher yields of crotonic acid would be expected on alkaline hydrolysis of the toluene-*p*-sulphonate (X) or methanesulphonate of ethyl β-hydroxybutyrate. This was found to be true. These derivatives were readily obtained by treatment of the hydroxy-ester with the appropriate sulphonyl chloride in pyridine, and under optimum conditions gave crotonic acid practically exclusively. The only simple β-sulphonyloxy-ester previously described appears to be ethyl β-toluene-*p*-sulphonyloxypropionate; this was reported by Clemo and Walton (*J.*, **1928**, 723) to be converted (in unspecified yield) into ethyl acrylate when treated with cold aqueous alkali. More recently, Eglinton and Whiting (*J.*, **1950**, 3650) have used the toluene-*p*-sulphonates of β-acetylenic alcohols for the preparation of vinylacetylenes, elimination occurring readily when the esters are heated with aqueous or alcoholic alkali.

The esters of other strong acids behaved similarly. The nitrate of β-hydroxybutyric acid (Duval, *Bull. Soc. chim.*, **1904**, **31**, 245) with diazomethane afforded the methyl ester (XI), which on alkaline hydrolysis gave crotonic acid in high yield. Ethyl β-hydroxybutyrate and diphenyl phosphorochloridate in pyridine gave the diphenyl phosphate (XII); hydrogenolysis of this over a platinum catalyst proceeded very slowly and was not complete, but the free phosphate (XIII) was separated from the mixture by conversion into the benzylamine salt, from which it was regenerated by interaction with a cation-exchange resin. Alkaline hydrolysis of the diphenyl phosphate gave a much higher yield of crotonic acid than was obtained from the phosphate. In an attempt to prepare the sulphate, ethyl β-hydroxybutyrate was treated with chlorosulphonic acid and pyridine, but only ethyl crotonate was obtained.

The greater tendency to elimination shown by the derivatives of the strong acids is significant. The elimination reaction must involve "alkyl–oxygen" fission at the β-position, and it is recognised that toluene-*p*-sulphonates and methanesulphonates readily undergo this type of cleavage; there is also evidence that esters of nitric acid can behave in the same way (J. W. Baker, *J.*, **1952**, 1193; see also Ansell and Honeyman, *J.*, **1952**,



2778). Simple aliphatic phosphates, acetates, and benzoates, however, usually undergo only acyl–oxygen fission under alkaline conditions, and the occurrence of alkyl–oxygen fission in their present reactions is of some interest, although establishment of the precise mechanism of the elimination is not at present possible.

Methyl α-methanesulphonyloxybutyrate, prepared from the α-hydroxy-ester, gave only a very small amount of crotonic acid when treated with alkali under conditions effective for the β-isomer; the elimination reaction is therefore characteristic of the β-hydroxy-ester derivatives.

Examination of ethyl 1-acetoxy*cyclo*hexylacetate (XIV) threw some light on the choice of position taken up by the double bond formed in elimination. The position of prototropic equilibrium between the corresponding unsaturated acids is 88% βγ $\rightleftharpoons$ 12% αβ (Linstead, *J.*, 1927, 362, 2579). Treatment of the acetate (XIV) with alkali under various conditions (none of which led to the dehydration of the free hydroxy-ester) led to some 25% of acyl elimination and the elimination product was exclusively the αβ-acid (XV). The formation of the labile isomer in this way contrasts with the dehydration of hydroxy*cyclo*hexylacetic ester which normally yields largely βγ-unsaturated material. Attempts in the present work to prepare the methanesulphonyloxy- and toluene-*p*-sulphonyloxy-ester gave only βγ-unsaturated ester.

Experiments with β-hydroxy-β-phenylpropionic acid (XVI) (Fittig and Slocum, *Annalen*, 1885, **227**, 59) showed an enhanced tendency for elimination, due to the additional conjugation of the double bond with phenyl. The β-hydroxy-acid itself was dehydrated to cinnamic acid by alkali under conditions where β-hydroxybutyric acid was unaffected. Furthermore, reaction of the ethyl ester with acetic anhydride resulted in the formation of much ethyl cinnamate; this was also the main product when the hydroxy-ester was treated with benzoyl chloride, methanesulphonyl chloride, or toluene-*p*-sulphonyl chloride in cold pyridine. However, the hydroxy-acid itself undergoes normal acetylation to give (XVII), and subsequent treatment with ethereal diazomethane gave methyl β-acetoxy-β-phenylpropionate (XVIII). Reaction of these compounds with alkali under mild conditions (when hydrolysis of the hydroxy-ester proceeded normally) gave cinnamic acid, the yield, as expected, being much greater from (XVIII) than from (XVII).

Different results were obtained when the phenyl group was in a more remote position. Ethyl β-hydroxy-δ-phenylvalerate reacted normally with acetyl or benzoyl chloride in pyridine, to give the derivatives (XXI), without any unsaturated product (compare the reactions of ethyl β-hydroxy-β-phenylpropionate, above). Alkaline hydrolysis of these derivatives gave a mixture of the hydroxy-acid (XX) and the αβ-unsaturated acid (XXII); as with the derivatives of 1-hydroxy*cyclo*hexylacetic ester, no βγ-unsaturated acid was detected. In this series of experiments, the yield of unsaturated acid was conveniently estimated by quantitative hydrogenation. Elimination occurred to a much smaller extent than with ethyl β-acetoxy-β-phenylpropionate; the ultimate formation of a highly conjugated system therefore favours the elimination reaction, probably because of the greater stability of the transition state.

Reaction of β-hydroxy-δ-phenylvaleric acid with acetic anhydride gave the acetoxy-anhydride (XXIII), which on treatment with aqueous alkali gave the αβ-unsaturated acid (XXII). On distillation, however, the anhydride gave a mixture of (XXII) and a different unsaturated acid, probably the βγ-unsaturated isomer (XXIV).

Finally it should be pointed out that in all the ester eliminations which have yielded unsaturated products of known configuration that configuration is *trans*. This is consistent with either a unimolecular or a bimolecular heterolytic mechanism. Further preliminary evidence bearing on the mechanism and stereospecificity of ester eliminations is given in Part II.

Experimental

Ethyl β-hydroxybutyrate, b. p. 74°/11 mm., n_D^{17} 1·4221, was prepared by hydrogenation of ethyl acetoacetate at room temperature and 50 atm. over Raney nickel. With the appropriate acid chloride in pyridine at 0° it gave ethyl β-acetoxybutyrate, b. p. 72°/0·4 mm., n_D^{20} 1·4284 (Found: equiv., 87·0. Calc. for $C_8H_{14}O_4$: equiv., 87), and ethyl β-benzoyloxybutyrate, b. p. 95°/3 × 10^{-4} mm. (slight decomp.), n_D^{19} 1·5000 (Found: equiv., 117·8. Calc. for $C_{13}H_{16}O_4$: equiv., 118).

Ethyl β-Methanesulphonyloxybutyrate.—A solution of the hydroxy-ester (40 g.) in pyridine (30 c.c.) was cooled to −5° and methanesulphonyl chloride (40 g.) in pyridine (40 c.c.) was added, with stirring, during 1·5 hours. The mixture was set aside at 0° for 12 hours, cooled to

−5°, and diluted with ice-water (220 c.c.); the precipitated oil was extracted with chloroform (3 × 60 c.c.), the extracts were washed with ice-cold 20% sulphuric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4) and evaporated. The residue on distillation afforded the *methanesulphonate* (52 g.), f. p. *ca.* 6°, b. p. 99°/10^{-4} mm. (Found: S, 15·2. $C_7H_{14}O_5S$ requires S, 15·2%), which soon became yellow.

The *toluene*-p-*sulphonate*, prepared as above from the hydroxy-ester (24 g.) and toluene-*p*-sulphonyl chloride (42 g.) in pyridine (80 c.c.), was a viscous non-distillable oil (37 g.) (Found: S, 11·1. $C_{13}H_{18}O_5S$ requires S, 11·2%).

Methyl β-*Nitratobutyrate*.—β-Nitratobutyric acid was prepared from sodium β-hydroxybutyrate (12 g.), fuming nitric acid (20 g.), and sulphuric acid (100 g.) at −15° (Duval, *Bull. Soc. chim.*, 1904, **31**, 245). The *methyl* ester, obtained with ethereal diazomethane, was an oil (6·6 g.), b. p. 94°/17 mm., n_D^{21} 1·4253 (Found: C, 37·0; H, 5·7; N, 8·5. $C_5H_9O_5N$ requires C, 36·8; H, 5·6; N, 8·6%).

Ethyl β-(*Diphenoxyphosphinyloxy*)*butyrate*.—To ethyl β-hydroxybutyrate (26·4 g.) in pyridine (40 c.c.), diphenyl phosphorochloridate (41·1 g.) (Brigl and Müller, *Ber.*, 1939, **72**, 2123) in pyridine (40 c.c.) was added at 0° during an hour. After 20 hours at 0° the mixture was diluted with ice-water (150 c.c.). The *diphenoxyphosphinyloxy*-derivative, isolated by chloroform extraction, was an oil (46 g.) which could be distilled in small quantities and had b. p. 120° (bath)/0·0003 mm., n_D^{23} 1·5319 (Found: C, 59·2; H, 5·95; P, 8·1. $C_{18}H_{21}O_6P$ requires C, 59·4; H, 5·9; P, 8·6%).

Ethyl β-*Phosphonyloxybutyrate*.—The foregoing ester (17·8 g.) and Adams' platinum catalyst (0·9 g.) in ethyl acetate (400 c.c.) were shaken with hydrogen at room temperature and pressure. Uptake was slow and incomplete. Evaporation of the filtered solution gave an oil (12·4 g.), n_D^{24} 1·4840 (Found: P, 10·6%); a portion (0·5 g.) in dry ether (8 c.c.) with benzylamine (0·5 g.) gave, after 2 hours at 0°, a precipitate (0·2 g.) which on crystallisation from benzene afforded the *dibenzylamine* salt, m. p. 144°, of ethyl β-phosphonyloxybutyrate (Found: N, 6·4. $C_{30}H_{31}O_6N_2P$ requires N, 6·6%).

A solution of this salt (0·5 g.) in water (40 c.c.) and ethanol (160 c.c.) was passed through a cation exchange column (Zeo-karb); evaporation under reduced pressure then gave the β-phosphonyloxy-ester as an acidic oil (0·2 g.) which was immediately used for the hydrolysis experiments; it rapidly decomposed on storage.

Control Hydrolysis of Ethyl β-*Hydroxybutyrate*.—Ethyl β-hydroxybutyrate (0·5 g.) when refluxed for 2 hours with 0·8N-sodium hydroxide (20 c.c.) in dioxan–water (1 : 1) afforded β-hydroxybutyric acid (0·3 g.) and no unsaturated material. The ester (13·2 g.) when refluxed for 12 hours with 2N-potassium hydroxide in aqueous ethanol (1 : 1) (100 c.c.) gave only β-hydroxybutyric acid (9·65 g., 93%).

Action of Alkali on the Derivatives of Ethyl β-*Hydroxybutyrate*.—(i) *Isolation experiments.* In a typical experiment ethyl β-acetoxybutyrate (10·55 g.) was refluxed for 4·5 hours with 0·8N-sodium hydroxide in aqueous dioxan (1 : 1) (185 c.c.); the solution was then partly neutralised with hydrochloric acid, concentrated under reduced pressure, acidified with hydrochloric acid, and continuously extracted with ether. The ethereal extract was washed once with an equal volume of water, dried (Na_2SO_4), and evaporated to yield crotonic acid (1·59 g., 30%) which crystallised from water in needles, m. p. and mixed m. p. 72°. The aqueous washing was continuously extracted with ether, and the extract dried (Na_2SO_4) and evaporated to an oil which was freed from acetic acid by storage *in vacuo* over potassium hydroxide. The residue (4·27 g.) was mainly β-hydroxybutyric acid, containing a little crotonic acid.

In some experiments, extraction with chloroform was used; this gave rather better recoveries of crotonic acid.

In the hydrolyses of the benzoate, the solution after removal of dioxan was acidified, cooled to 0°, and filtered from precipitated benzoic acid before extraction.

In the hydrolysis of the diphenyl phosphate, the ethereal extract, containing crotonic acid, β-hydroxybutyric acid, and phenol, was washed with sodium hydrogen carbonate to remove the acids, which were then recovered by acidification and extraction, and separated in the usual way.

(ii) *Titrimetric experiments.* A known weight (*ca.* 0·5 g.) of the appropriate ester was refluxed with excess of alkali as in the isolation experiments, cooled, and diluted to 100 c.c. Aliquots (25 c.c.) were acidified with hydrochloric acid, treated with 50 c.c. of 0·1N-potassium bromate containing an excess of potassium bromide, and kept for 15 minutes in the dark; potassium iodide (200% excess) was then added and the iodine titrated with sodium thiosulphate.

Ethyl α-Methanesulphonyloxybutyrate.—Treatment of ethyl α-hydroxybutyrate (1·5 g.) in pyridine (10 c.c.) with methanesulphonyl chloride (1·5 g.) for 16 hours at 0°, as described for the β-isomer, gave the *methanesulphonate* (1·7 g.), b. p. 65°/0·005 mm., n_D^{18} 1·4363 (Found: C, 40·15; H, 6·9. $C_7H_{14}O_5S$ requires C, 40·0; H, 6·7%).

Alkaline hydrolysis. The α-methanesulphonate (0·5 g.) was boiled under reflux for 4 hours with N-sodium hydroxide in 1 : 1 aqueous dioxan (10 c.c.). The yield of crotonic acid, estimated by the bromine addition method described above, was 8%.

Control Hydrolysis of Ethyl 1-Hydroxycyclohexylacetate.—Ethyl 1-hydroxy*cyclo*hexylacetate (18·6 g.) (*Org. Reactions*, **1**, 17) when refluxed for 8 hours with N-sodium hydroxide (300 c.c.) in aqueous ethanol (1 : 1) afforded 1-hydroxy*cyclo*hexylacetic acid (12·1 g., 90%) and no unsaturated material. Recrystallisation from benzene–light petroleum afforded the hydroxy-acid (9·8 g.), m. p. and mixed m. p. 64°.

Action of Alkali on Ethyl 1-Acetoxycyclohexylacetate.—In a typical experiment the acetoxy-ester (5·0 g.), b. p. 116—118°/4 mm., n_D^{25} 1·4557 (Auwers and Ellinger, *Annalen*, 1912, **387**, 228), was set aside for 48 hours with 100 c.c. (10% excess) of 0·5N-potassium hydroxide in aqueous methanol (1 : 1); the solution was then acidified with 2N-hydrochloric acid (50 c.c.) and diluted to 250 c.c., and the unsaturated acids were removed by exhaustive steam-distillation. The distillate was extracted with ether (4 × 50 c.c.), and the extract dried (Na_2SO_4) and evaporated to a solid residue, m. p. 87—88° (0·75 g., 24%). Crystallisation from aqueous ethanol gave needles of *cyclo*hexylideneacetic acid, m. p. and mixed m. p. 90°. The crude material was shown to contain no βγ-isomer by the iodine-addition method of Linstead and May (*J.*, 1927, 2567), the absorption being only 2·9%. The residue from the steam-distillation was continuously extracted with ether and gave 1-hydroxy*cyclo*hexylacetic acid (1·2 g.), which after crystallisation from benzene–light petroleum had m. p. and mixed m. p. 64°.

Reaction of Ethyl 1-Acetoxycyclohexylacetate with Sodium Ethoxide.—The ester (15 g.) was boiled under reflux for 17 hours with 0·1N-sodium ethoxide in ethanol (1500 c.c.), cooled, and diluted with water (100 c.c.). The excess of alkali was neutralised with carbon dioxide, the sodium carbonate filtered off, and the filtrate evaporated under reduced pressure to 500 c.c. Water (1 l.) was added, the solution was extracted with ether (3 × 200 c.c.), and the extract was dried ($MgSO_4$) and evaporated. The residue (6·3 g.) on fractionation gave (i) unsaturated ester (2·0 g.), b. p. 62—70°/1 mm., n_D^{20} 1·4790, and (ii) hydroxy-ester (4·1 g.) b. p. 94—100°/1 mm., n_D^{20} 1·4681. The iodine-addition value of (i) was 4·9%. Linstead and May (*loc. cit.*) give 4·2 ± 0·5% for ethyl *cyclo*hexylideneacetate, and record n_D^{18} 1·4799.

The aqueous solution was acidified and the acids were evaporated by steam-distillation, to give the αβ-unsaturated acid (0·4 g.) (iodine addition, 2·4%) and the β-hydroxy-acid (0·9 g.).

Reaction of Ethyl 1-Hydroxycyclohexylacetate with Toluene-p-sulphonyl Chloride.—The chloride (1·3 g.) was added during ½ hour to the ester (1 g.) in pyridine (10 c.c.) at 0°. After 6 days at 0°, ice-water was added and the product was extracted with chloroform, washed with cold 2N-sulphuric acid, sodium hydrogen carbonate, and water, and isolated by evaporation. The residual oil (0·9 g.) on distillation afforded only ethyl *cyclo*hexenylacetate (0·83 g.), b. p. 66°/0·7 mm., n_D^{22} 1·4622 (Kon and Linstead, *J.*, 1929, 1278, give n_D^{24} 1·4621).

Methyl β-Acetoxy-β-phenylpropionate.—β-Acetoxy-β-phenylpropionic acid (Fittig and Slocum, *Annalen*, 1885, **227**, 59) with ethereal diazomethane gave the *methyl* ester, b. p. 84°/0·03 mm., n_D^{25} 1·5139 (Found: C, 65·4; H, 6·45. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·35%).

Control Hydrolysis of Methyl β-Hydroxy-β-phenylpropionate.—The ester (1·8 g.) was kept with N-sodium hydroxide (25 c.c.) in 1 : 1 aqueous methanol at room temperature for 48 hours; water (20 c.c.) was then added and the alkali neutralised with hydrochloric acid. The methanol was removed under reduced pressure, and the solution acidified and cooled to 0°; no precipitation of cinnamic acid occurred. Extraction with ether (3 × 10 c.c.) gave the β-hydroxy-acid (1·4 g., 84%) which on crystallisation from water had m. p. 100°.

Similar experiments with ethyl β-hydroxy-β-phenylpropionate showed that no cinnamic acid was formed when the ester was hydrolysed under reflux with (i) N-barium hydroxide, (ii) N-sodium carbonate, (iii) 0·1N-potassium hydroxide, all in 1 : 1 ethanol–water. When, however, the ester was hydrolysed with boiling aqueous-alcoholic (1 : 1) 2N-potassium hydroxide, acidification of the solution (after removal of ethanol) gave a precipitate of cinnamic acid (yield, 10%), m. p. 133° after recrystallisation from water.

Action of Alkali on β-Acetoxy-β-phenylpropionic Acid.—In a typical experiment the β-acetoxy-acid (1·0 g.) was dissolved in N-sodium carbonate (11 c.c.), heated on the steam-bath for 2½ hours, cooled to 0°, acidified with concentrated hydrochloric acid, and set aside at 0° for 1 hour. The precipitated cinnamic acid (0·08 g., 11%), on recrystallisation from water, had

m. p. and mixed m. p. 133°. The main filtrate was extracted with ether (3 × 8 c.c.), and the extract dried (Na_2SO_4), evaporated and freed from acetic acid by storage *in vacuo* over potassium hydroxide. The residue of hydroxy-acid (0·59 g., 76%), when recrystallised from water, had m. p. and mixed m. p. 100°.

Action of Alkali on Methyl β-Acetoxy-β-phenylpropionate.—The ester (*ca.* 1 g.) was treated with alkali (2·2 equiv.) in aqueous methanol (1 : 1) under the conditions indicated in the Table. The alkali was then exactly neutralised (phenolphthalein) with N-hydrochloric acid, the methanol removed under reduced pressure, and any neutral material extracted with ether. The solution was then acidified and the acid products isolated as previously described.

In a typical experiment, the ester (1·0 g.) when set aside at room temperature for 48 hours with N-sodium hydroxide in aqueous methanol (1 : 1) (10 c.c.) gave cinnamic acid (0·36 g., 54%) and hydroxy-acid (0·29 g., 38%).

Methyl β-Hydroxy-δ-phenylvalerate.—β-Hydroxy-δ-phenylvaleric acid (Farmer and Hose, *J.*, 1933, 962) with methanol and sulphuric acid gave the *methyl* ester, b. p. 114—116°/0·5 mm., n_D^{20} 1·5100 (Found: C, 69·1; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

Ethyl β-Acetoxy-δ-phenylvalerate.—Ethyl β-hydroxy-δ-phenylvalerate (Farmer and Hose, *loc. cit.*) (11 g.), acetyl chloride (8·5 g.), and pyridine (25 c.c.) were mixed and kept at 0° for 6 hours; ice-water (100 c.c.) was then added and the oil was extracted into chloroform (3 × 20 c.c.), washed with 2N-sulphuric acid and with water, dried (Na_2SO_4), and evaporated, and the residue distilled to give *ethyl β-acetoxy-δ-phenylvalerate* (10 g.), b. p. 100°/10^{-5} mm. (Found: C, 68·4; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

Ethyl β-Benzoyloxy-δ-phenylvalerate.—The hydroxy-ester (11 g.) in pyridine (25 c.c.) on similar treatment with benzoyl chloride (7·8 g.) gave the *benzoate* (15 g.), a viscous oil, b. p. 120°/10^{-5} mm., which solidified (needles) on storage (m. p. *ca.* 25°) (Found: C, 73·5; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

5-Phenylpent-2-enoic Acid (CO_2H = 1).—Distillation of β-hydroxy-δ-phenylvaleric acid at 160°/1·0 mm. furnished 5-phenylpent-2-enoic acid, which after crystallisation from water had m. p. 104° (Farmer and Hose, *loc. cit.*, give m. p. 103°).

Control Hydrolysis of Ethyl β-Hydroxy-δ-phenylvalerate.—Treatment of the ester with an excess of aqueous alcoholic alkali, under the conditions specified below, gave only the hydroxy-acid, m. p. 130°, and no unsaturated material: (i) 0·25N-KOH at room temperature; (ii) N-Na_2CO_3 at room temperature; (iii) 0·1N-KOH under reflux; (iv) 0·5N-Na_2CO_3 under reflux.

With boiling 0·5N-sodium hydroxide, some unsaturated acid, m. p. 90°, was formed, possibly 5-phenylpent-4-enoic acid (Farmer and Hose, *loc. cit.*, give m. p. 90°).

Action of Alkali on Ethyl β-Acetoxy-δ-phenylvalerate.—The acetoxy-ester (2·5 g.) was treated with 0·2N-potassium hydroxide in 1 : 1 aqueous ethanol (100 c.c.) at room temperature for 48 hours; the solution was then neutralised with hydrochloric acid, ethanol removed under reduced pressure, and the solution acidified and extracted with ether (3 × 15 c.c.). The extract was dried (Na_2SO_4) and evaporated, and the residue (1·6 g.) was extracted with carbon disulphide. The insoluble portion (0·6 g.), β-hydroxy-δ-phenylvaleric acid, after crystallisation from water had m. p. and mixed m. p. 130°. The carbon disulphide extract was evaporated and the solid extracted with light petroleum (b. p. 60—80°); the insoluble material (0·67 g.) was more of the β-hydroxy-acid. The petroleum extract on evaporation gave 5-phenylpent-2-enoic acid (0·2 g.) which after recrystallisation from water had m. p. and mixed m. p. 103°.

Action of Alkali on Ethyl β-Acetoxy(and β-Benzoyloxy)-δ-phenylvalerate and Estimation of the Unsaturated Products by Catalytic Hydrogenation.—The ester (*ca.* 0·8 g.) was treated with alkali (2·2 equiv.) in aqueous ethanol (1 : 1) under various conditions (see Table); the excess of alkali was then neutralised, the ethanol evaporated under reduced pressure, and the solution acidified strongly with hydrochloric acid and extracted thrice with ether. The extract was dried (Na_2SO_4) and evaporated, and the solid residue dissolved in ethanol and hydrogenated at room temperature over palladium–charcoal. The proportion of unsaturated acid was then calculated from the amount of hydrogen absorbed. The filtered solution was evaporated and the residue was extracted with carbon disulphide; the insoluble portion was β-hydroxy-δ-phenylvaleric acid, m. p. 130° (after recrystallisation from water). The δ-phenylvaleric acid, recovered from the carbon disulphide solution, crystallised from water in plates, m. p. 58°.

Anhydride of β-Acetoxy-δ-phenylvaleric Acid.—A mixture of β-hydroxy-δ-phenylvaleric acid (1·1 g.) and acetic anhydride (10 c.c.) was heated at 80° for 2½ hours and then evaporated under reduced pressure, to give the *acetoxy-anhydride* as a neutral oil (1·1 g.), which was saturated to aqueous permanganate, and dissolved slowly in hot 2N-sodium hydroxide (Found: C, 69·2; H, 6·8. $C_{28}H_{30}O_7$ requires C, 68·7; H, 6·7%). Distillation of a portion (0·5 g.) at 140°/1 mm.

gave an oil which partly solidified. The solid (0·2 g.) was sublimed at 115°/0·4 mm., and then crystallised from water to give 5-phenylpent-2-enoic acid, m. p. 98°, not depressed on admixture with the pure acid, m. p. 104° (Found: C, 75·0; H, 6·9. Calc. for $C_{11}H_{12}O_2$: C, 75·0; H, 6·9%). The liquid portion (0·2 g.) slowly solidified and had m. p. 28° (Farmer and Hose, *loc. cit.*, give m. p. 30° for 5-phenylpent-3-enoic acid).

Treatment of the anhydride (0·28 g.) with 0·1N-potassium hydroxide (50 c.c.) at 90° for 1½ hours, followed by concentration, acidification, and extraction with ether, gave 5-phenylpent-2-enoic acid, m. p. and mixed m. p. 104°.

Micro-analyses in this and the two following papers were carried out in the Micro-analytical Laboratory of this Department (Mr. F. H. Oliver).

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244. *Elimination Reactions of Esters. Part II.* The Formation of α-Keto-acids from Derivatives of αβ-Dihydroxy-acids, and Related Reactions.*

By R. P. Linstead, L. N. Owen, and R. F. Webb.

The action of alkali on αβ-diacyloxy-butyric and -β-phenylpropionic esters has been studied. The diacetates undergo normal hydrolysis, without elimination, but the dimethanesulphonates and ditoluene-*p*-sulphonates on mild treatment give the α-sulphonyloxy-crotonic or -cinnamic acids, by preferential elimination from the β-position. These products, on further alkaline hydrolysis, yield the corresponding α-keto-acids. The *erythro*- and the *threo*-forms of the αβ-disulphonyloxybutyrates give stereoisomeric α-sulphonyloxycrotonic acids, but only one α-sulphonyloxycinnamic acid is obtained from a pair of stereoisomeric β-phenyl-αβ-disulphonyloxypropionates.

Reaction of the disulphonates with sodium iodide yields crotonic or cinnamic acid by *cis*-elimination, *erythro- and threo*-disulphonates giving *cis*- and *trans*-products, respectively.

In the preceding paper it was shown that certain derivatives, $\rangle C(OR)\cdot CH_2\cdot CO_2Et$, of β-hydroxy-esters, in which the hydroxyl group was itself esterified, underwent elimination on alkaline hydrolysis to yield the αβ-unsaturated acid $\rangle C{:}CH\cdot CO_2H$, the yield of which was greatest when R was methanesulphonyl, toluene-*p*-sulphonyl, or nitro. The present communication is concerned with similar investigations on derivatives of αβ-dihydroxy-esters, which, since elimination would be expected to occur preferentially from the β-position, were expected to yield α-keto-acids through their enols [route (*a*)]:

$$\rangle C(OR)\cdot CH(OR)\cdot CO_2Et \xrightarrow{(a)} \rangle C{:}C(OR)\cdot CO_2H \longrightarrow \rangle C{:}C(OH)\cdot CO_2H \longrightarrow \rangle CH\cdot CO\cdot CO_2H$$

$$\rangle C(OR)\cdot CH(OH)\cdot CO_2H \quad (b)$$

This was confirmed, and evidence was also obtained to show that the reaction did not proceed by the less likely route (*b*).

Methyl *erythro*-αβ-dihydroxybutyrate, treated in pyridine with acetic anhydride, methanesulphonyl chloride, and toluene-*p*-sulphonyl chloride, severally, gave the liquid diacetate, and the solid disulphonates (III).† An alternative method for the ditoluene-*p*-sulphonate (III) involved conversion of crotonic acid *via* the chlorohydrin into the *threo*-epoxide, the methyl ester (I) of which was treated with toluene-*p*-sulphonic acid to give an oily monohydroxy-monotoluene-*p*-sulphonate. It was not established whether ring-fission had occurred exclusively in one direction, though from analogy with the corre-

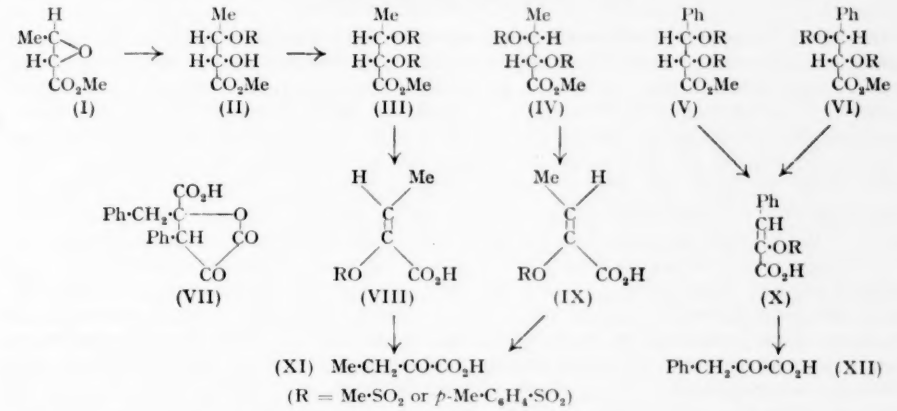
* Part I, preceding paper.

† Formulæ (I—VI) and (XIII—XV) represent, of course, optically active forms; the actual compounds used in this work were racemic.

sponding reaction of phenylglycidic acid (see below) the product was probably mainly the β-sulphonate (II); further reaction with toluene-*p*-sulphonyl chloride gave the *erythro*-ditoluene-*p*-sulphonate (III), this stereochemical result being in accordance with the occurrence of the usual inversion during the fission of an epoxide.

Methyl *threo*-αβ-dihydroxybutyrate was obtained by *cis*-hydroxylation of methyl crotonate with buffered aqueous permanganate at low temperature; it gave the solid disulphonates (IV).

Hydrolysis of the *erythro*-diacetate with concentrated aqueous-alcoholic alkali gave only the *erythro*-dihydroxy-acid; no keto-acid could be detected. The four sulphonates (III) and (IV), however, all gave α-ketobutyric acid (XI), and by the use of cold dilute alkali it was possible to stop the reaction at the intermediate stage; each disulphonate then gave a different crystalline unsaturated monosulphonate, all of which on further alkaline hydrolysis gave (XI), thus proving that the monosulphonates were α-substituted crotonic acids and confirming the expected preferential elimination of the β-substituent in an αβ-disulphonyloxy-ester. It seems likely that a bimolecular mechanism is involved, since a unimolecular process, involving an intermediate carbonium ion, would probably not result in the formation of a different monosulphonate from each disulphonate. Furthermore, on the assumption that *trans*-elimination occurs, an *erythro*- and a *threo*-disulphonate

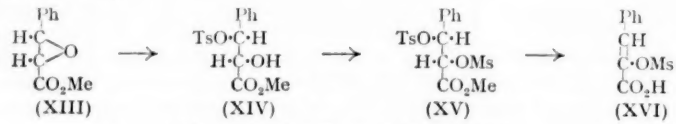


will give respectively a *cis*- and a *trans*-α-sulphonyloxycrotonic acid. The *cis*-configuration (VIII) can therefore be allocated to the methanesulphonate, m. p. 112—113°, and the toluene-*p*-sulphonate, m. p. 118°, derived from the *erythro*-esters (III); and the *trans*-configuration (IX) to the methanesulphonate, m. p. 94—95°, and the toluene-*p*-sulphonate, m. p. 138°, from (IV).

From the *erythro*- and the *threo*-isomer of methyl αβ-dihydroxy-β-phenylpropionate, with the appropriate acid chloride in pyridine, the four crystalline disulphonates (V) and (VI) were obtained. Alkaline hydrolysis of the diacetyl and the dibenzoyl derivative of *threo*-αβ-dihydroxy-β-phenylpropionic acid gave only the *threo*-dihydroxy-acid, but the sulphonates again underwent elimination. In this series, however, an interesting difference from the behaviour of the dihydroxybutyric derivatives was observed, in that the same unsaturated monosulphonate (X) was formed from each of the corresponding disulphonates (V) and (VI); further alkaline hydrolysis of the monomethane- and mono-toluene-*p*-sulphonate gave phenylpyruvic acid (XII), and reaction of methyl phenylpyruvate with toluene-*p*-sulphonyl chloride in pyridine gave methyl α-toluene-*p*-sulphonyloxycinnamate, identical with the product obtained by treatment of the toluene-*p*-sulphonate (X) with diazomethane. This established the structures of (X), though in this series the configurations, which are probably *trans*, clearly cannot be deduced from those of their precursors, and the mechanism of elimination may differ from that in the dihydroxybutyric series. When the disulphonates (VI) were hydrolysed with concentrated methanolic potassium

hydroxide a weakly acidic product was obtained which, when separated from polymer, was identified as the "di(phenylpyruvic) acid" (VII) described by Jarrousse (*Ann. Chim.*, 1938, **9**, 157).

Reaction of methyl αβ-epoxy-β-phenylpropionate (prepared by the Darzens condensation of benzaldehyde with methyl chloroacetate) with toluene-*p*-sulphonic acid gave a crystalline monohydroxy-monotoluene-*p*-sulphonate which was shown to be (XIV) from the following observations. Toluene-*p*-sulphonation gave the *threo*-ditoluene-*p*-sulphonate (VI; R = *p*-Me·C_6H_4·SO_2), thus establishing the configuration, whilst methanesulphonation gave a methanesulphonate–toluene-*p*-sulphonate which on reaction with alkali furnished the α-methanesulphonyloxycinnamic acid (XVI); the mixed derivative must therefore be (XV) and hence the monotoluene-*p*-sulphonate is the β-derivative (XIV). It follows, from the *threo*-configuration of (XIV), that the epoxide must have been mainly the *erythro*-form (XIII).



(Ms = Me·SO_2; Ts = *p*-Me·C_6H_4·SO_2)

In view of the general similarity between the reactions of sulphonyl esters and those of halides, it is interesting to compare some of the reactions described above with those of the corresponding bromo-acids. It is well established that reaction of *erythro*-αβ-dibromobutyric acid, or its esters, with aqueous or alcoholic alkali, gives almost entirely *cis*-α-bromocrotonic acid (*inter al.*, James, *J.*, 1910, **97**, 1572); the *threo*-dibromo-acid is reported to give a mixture of *cis*- and *trans*-β-bromocrotonic acid (Michael and Schulthess, *J. pr. Chem.*, 1892, **46**, 263), but further confirmation is desirable. With the αβ-dibromo-β-phenylpropionic acids and esters the composition of the product is greatly influenced by the nature of the reaction medium, but it is of interest that the stereoisomeric methyl esters, on treatment with alcoholic alkali, give mainly the same *trans*-α-bromocinnamic acid (Sudborough and Thompson, *J.*, 1903, **83**, 666; James and Sudborough, *J.*, 1909, **95**, 1541). Broadly, therefore, in both series, the reactions are similar to those shown in the first stage of the hydrolysis of the sulphonates. In the second stage, however, there are some important points of difference, because, although *cis*- or *trans*-α-bromocrotonic acid on further reaction with aqueous alkali behaves like the corresponding α-sulphonate and gives α-ketobutyric acid (Owen, *J.*, 1945, 385), the α-bromocinnamic acids do not give phenylpyruvic acid but undergo further elimination to yield phenylpropiolic acid. Strong evidence has been presented that substitution of the halogen in αβ-unsaturated α-bromo-acids not does occur directly, but only after an initial prototropic change (Owen and Sultanbawa, *J.*, 1949, 3089), and the behaviour of α-bromocinnamic acid, which cannot undergo the initial isomerisation, is therefore understandable (see also Newman and Owen, *J.*, 1952, 4722). The formation of phenylpyruvic acid from the α-sulphonyloxycinnamic acids therefore suggests the operation of a mechanism different from that postulated for the bromo-acids. In the hydrolysis of a halide, the breaking of the carbon–halogen bond corresponds to the "alkyl–oxygen" fission of an ester, and is of course the only type possible. Now although esters of sulphonic acids usually undergo this form of fission (which explains why their reactions are often similar to those of halides), it seems likely that in circumstances where "alkyl–oxygen" fission is inhibited the "acyl–oxygen" type R–O–$\overset{|}{\underset{|}{}}$–Ts may operate (cf. Ferns and Lapworth, *J.*, 1912, **101**, 273). This would explain why the reactions of the disulphonates (VI) with methanolic potassium hydroxide gave only phenylpyruvic acid and no α-methoxycinnamic acid.

The availability of the sulphonyl derivatives of the αβ-dihydroxy-butyric and -β-phenylpropionic esters led us to examine their behaviour towards sodium iodide, since with this reagent a compound containing sulphonyloxy-groups attached to two vicinal carbon atoms, one of which is primary, *e.g.*, R·CH(OTs)·CH_2·OTs, gives the unsaturated product R·CH:CH_2 (cf. Bladon and Owen, *J.*, 1950, 598; Foster and Overend, *J.*, 1951,

3452) whereas if both groups are secondary they are usually resistant to such treatment (for examples, see Bell and Synge, *J.*, **1937**, 1711; Bacon, Bell, and Lorber, *J.*, **1940**, 1147). The dimethanesulphonates (III), (IV), (V), and (VI), however, all reacted slowly with sodium iodide in boiling acetone to give methyl *cis*-crotonate, methyl *trans*-crotonate, methyl *cis*-cinnamate, and methyl *trans*-cinnamate, respectively. These stereochemical results are of much interest, in that the *erythro*- and *threo*-esters give *cis*- and *trans*-products respectively, *i.e.*, the overall result is one of *cis*-elimination. This is the opposite to the debromination of dibromides with potassium iodide (cf. Crombie, *Quart. Reviews*, **1952**, **6**, 101); thus *erythro*-αβ-dibromo-butyric and -β-phenylpropionic acids give *trans*-crotonic and *trans*-cinnamic acid, respectively (Erlenmeyer and Müller, *Ber.*, **1882**, **15**, 49; van Duin, *Rec. Trav. chim.*, **1926**, **45**, 347). The reaction is being studied in more detail, and, if of more general application, may provide a valuable method for changing the configuration of double bonds by the sequence :

$$\textit{trans}\text{-Olefin} \xrightarrow[\text{Hydroxylation}]{\textit{trans}\text{-}} \textit{cis}\text{-Diol} \longrightarrow \textit{cis}\text{-Disulphonate} \longrightarrow \textit{cis}\text{-Olefin}$$

Experimental

Methyl erythro-αβ-*Dihydroxybutyrate.*—*erythro*-αβ-Dihydroxybutyric acid, m. p. 82—83°, prepared by catalytic hydroxylation of crotonic acid with aqueous pertungstic acid at 70° (Mugdan and Young, *J.*, 1949, 2999), was treated in methanol with excess of ethereal diazomethane. Removal of solvent under reduced pressure gave the methyl ester, which was used without further purification.

Methyl threo-αβ-*Dihydroxybutyrate.*—To methyl crotonate (66·5 g.) in ethanol (3 l.) at −40°, a solution of potassium permanganate (127 g.) and magnesium sulphate heptahydrate (100 g.) in water (4 l.) was added with vigorous stirring during 5 hours. The mixture was then allowed to attain room temperature, and the filtered solution was concentrated (to 2 l.) and continuously extracted with ether; evaporation of the dried extracts gave the methyl ester (14 g.).

Methyl αβ-*Epoxybutyrate.*—β-Methylglycidic acid (5 g.), m. p. 88° (Braun, *J. Amer. Chem. Soc.*, 1930, **52**, 3185), with an excess of ethereal diazomethane afforded the *methyl* ester (4·9 g.), b. p. 160—161°, n_D^{18} 1·4205 (Found : C, 51·5; H, 7·0. $C_5H_8O_3$ requires C, 51·7; H, 7·0%).

Derivatives of Methyl erythro-αβ-*Dihydroxybutyrate.*—(i) The ester (1·1 g.), acetic anhydride (2·4 c.c.), and pyridine (6 c.c.) were kept at 0° for 12 hours. The solution was then diluted with ice-water and extracted with chloroform, the extract washed with 2N-sulphuric acid, and with water, dried, and evaporated, and the residue distilled, affording *methyl* erythro-αβ-*diacetoxybutyrate* (0·75 g.), b. p. 85°/0·01 mm., n_D^{20} 1·4289 (Found : C, 49·7; H, 6·6. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5%).

(ii) The ester (6·7 g.) in pyridine (25 c.c.) was cooled to −5°, and toluene-*p*-sulphonyl chloride (20 g.) in pyridine (90 c.c.) was added during 1½ hours. After 16 hours at 0° ice-water (230 c.c.) was added, and the product was isolated by chloroform extraction as described for the diacetate. It was an oil which on trituration with methanol slowly deposited crystals (9·45 g.), m. p. 59—63°. Recrystallisation from an equal volume of methanol gave *methyl* erythro-αβ-*ditoluene*-p-*sulphonyloxybutyrate*, m. p. 73° (Found : C, 51·9; H, 5·2; S, 14·5. $C_{19}H_{22}O_6S_2$ requires C, 51·6; H, 5·0; S, 14·5%).

(iii) Similar treatment of the ester (13·3 g.) in pyridine (20 c.c.) with methanesulphonyl chloride (18 c.c.) in pyridine (80 c.c.) gave needles (18·1 g.) (from methanol) of *methyl* erythro-αβ-*dimethanesulphonyloxybutyrate*, m. p. 63—64° (Found : C, 29·3; H, 4·9; S, 22·1. $C_7H_{14}O_8S_2$ requires C, 29·0; H, 4·9; S, 22·1%).

Derivatives of Methyl threo-αβ-*Dihydroxybutyrate.*—Prepared as described for the *erythro*-isomers, the *ditoluene*-p-*sulphonate* formed needles (from methanol), m. p. 90° (Found : C, 51·1; H, 5·0; S, 14·3%), and the *dimethanesulphonate* needles (from methanol), m. p. 128° (Found : C, 29·1; H, 4·8; S, 21·9%).

Reaction of Methyl αβ-*Epoxybutyrate with Toluene*-p-*sulphonic Acid.*—A solution of the ester (2·3 g.) and toluene-*p*-sulphonic acid (3·5 g.) in dry ether was set aside at room temperature overnight and then evaporated to an oil. A portion (0·3 g.), on treatment with toluene-*p*-sulphonyl chloride in pyridine, gave a solid (0·2 g.), which when recrystallised from methanol afforded methyl *erythro*-αβ-ditoluene-*p*-sulphonyloxybutyrate, m. p. and mixed m. p. 73°.

Alkaline Hydrolysis of Methyl erythro-αβ-*Diacetoxybutyrate.*—A solution of the ester (1 g.) and potassium hydroxide (1 g.) in water (3 c.c.) and ethanol (12 c.c.) was boiled under reflux

for 2 hours, then cooled and passed through a cation-exchange column ("Amberlite"). Elution with ethanol, and evaporation, gave a syrup which gave no ketonic reactions and slowly crystallised to give *erythro*-αβ-dihydroxybutyric acid (0·3 g.), m. p. and mixed m. p. 81—82° (from ethyl acetate). The alcoholic distillate, also, was free from ketonic material.

Reactions of the Methyl αβ-Disulphonyloxybutyrates with Aqueous Alkali.—(i) The *erythro*-ditoluene-*p*-sulphonate (4·1 g.) in dioxan (75 c.c.) was added to potassium hydroxide (3·4 g.) in water (25 c.c.); the mixture was vigorously stirred for 18 hours at room temperature, diluted with water (100 c.c.), and then neutralised with carbon dioxide. The dioxan was removed below 50°, and the aqueous solution acidified with hydrochloric acid and extracted with ether (3 × 60 c.c.). Evaporation of the dried (Na_2SO_4) extracts gave cis-α-*toluene*-p-*sulphonyloxycrotonic acid* (2·2 g.), which crystallised from carbon tetrachloride in rosettes of needles, m. p. 118° (Found: C, 51·7; H, 4·8; S, 12·6. $C_{11}H_{12}O_5S$ requires C, 51·6; H, 4·7; S, 12·5%).

(ii) The *erythro*-dimethanesulphonate (11·6 g.) in dioxan (250 c.c.) with potassium hydroxide (7·0 g.) in water (150 c.c.) similarly gave cis-α-*methanesulphonyloxycrotonic acid* (2·9 g.) which crystallised from chloroform–carbon tetrachloride in needles, m. p. 112—113° (Found: C, 33·5; H, 4·4; S, 17·5. $C_5H_8O_5S$ requires C, 33·4; H, 4·5; S, 17·8%).

The acidic aqueous residue was continuously extracted with ether for 48 hours, and the extract dried ($MgSO_4$) and evaporated to an oil (2·2 g.), mainly α-ketobutyric acid. A portion (0·2 g.) with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate gave a yellow precipitate (0·4 g.) which when recrystallised from aqueous ethanol gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 195°.

(iii) The *threo*-ditoluene-*p*-sulphonate (8·2 g.) with potassium hydroxide (6·8 g.), water (50 c.c.), and dioxan (150 c.c.) gave trans-α-*toluene*-p-*sulphonyloxycrotonic acid* (2·4 g.), m. p. 138° (from benzene) (depressed to 104—113° on admixture with the isomer of m. p. 118°) (Found: C, 51·8; H, 4·8; S, 13·0%), and α-ketobutyric acid (1·9 g.).

(iv) The *threo*-dimethanesulphonate (8·7 g.) with potassium hydroxide (5·0 g.) in water (37 c.c.) and dioxan (180 c.c.) gave trans-α-*methanesulphonyloxycrotonic acid* (4·2 g.), which crystallised from benzene in needles, m. p. 94—95° (depressed to 83—86° on admixture with the isomer of m. p. 112—113°) (Found: C, 33·2; H, 4·6; S, 17·1%).

Reactions of the α-Sulphonyloxycrotonic Acids with Aqueous Alkali.—*cis*-α-Methanesulphonyloxycrotonic acid (0·18 g.) was boiled under reflux for 1 hour with N-sodium hydroxide (2 c.c.). The cooled solution was diluted with water (20 c.c.) and 2N-sulphuric acid (4 c.c.), and a standard solution (15 c.c.) of 2 : 4-dinitrophenylhydrazine sulphate was added (1·5 g. of base in 200 c.c. of concentrated sulphuric acid diluted to 1 l. with water). The yellow precipitate (0·14 g.) was collected, washed with 2N-sulphuric acid and with water, and dried at 100°. Crystallisation from aqueous ethanol afforded the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 195°, of α-ketobutyric acid.

trans-α-Methanesulphonyloxycrotonic acid (0·18 g.), and the *cis*- and the *trans*-α-toluene-*p*-sulphonyloxycrotonic acid (0·26 g. each), on similar treatment all gave the 2 : 4-dinitrophenylhydrazone, m. p. 195° (yields, 0·14, 0·21, and 0·16 g., respectively).

Methyl erythro-αβ-*Dihydroxy*-β-*phenylpropionate.*—Treatment of the dihydroxy-acid, m. p. 121° (Böeseken, *Rec. Trav. chim.*, 1922, **41**, 206) with ethereal diazomethane gave the methyl ester, m. p. 87° (from carbon tetrachloride).

Methyl threo-αβ-*Dihydroxy*-β-*phenylpropionate.*—Methyl cinnamate (80 g.) in ethanol (6 l.) was oxidised at −40° by addition of potassium permanganate (96 g.) and magnesium sulphate heptahydrate (100 g.), in water (3 l.). The mixture was worked up as described for the oxidation of methyl crotonate, and gave the *threo*-dihydroxy-ester, which crystallised from carbon tetrachloride in needles (68 g.), m. p. 69°.

Derivatives of Methyl erythro- *and* threo-αβ-*Dihydroxy*-β-*phenylpropionate.*—Treatment of the esters with the appropriate acid chloride in pyridine at 0°, as described for the dihydroxybutyric derivatives, gave solid products on dilution of the reaction mixtures with ice-water. Recrystallisation (from methanol in each case) gave the erythro-*ditoluene*-p-*sulphonate*, m. p. 132° (Found: C, 57·3; H, 4·8; S, 12·5. $C_{24}H_{24}O_8S_2$ requires C, 57·1, H, 4·8; S, 12·7%); the threo-*ditoluene*-p-*sulphonate*, m. p. 132° (Found: C, 57·0; H, 4·7; S, 12·4%) (depressed to *ca.* 120° on admixture with the *erythro*-isomer); the erythro-*dimethanesulphonate*, m. p. 118—119° (Found: C, 41·1; H, 4·6; S, 18·1. $C_{12}H_{16}O_8S_2$ requires C, 40·9; H, 4·6; S, 18·2%); and the threo-*dimethanesulphonate*, m. p. 110° (Found: C, 40·9; H, 4·6; S, 18·2%).

Methyl αβ-*Epoxy*-β-*phenylpropionate.*—Benzaldehyde (106 g.) and methyl chloroacetate (109 g.) in benzene (200 c.c.) were cooled in ice–salt, and dry, powdered sodium methoxide (70 g.) was added, with vigorous stirring, during 4 hours. Stirring was then maintained for

16 hours at room temperature and the product was poured on crushed ice (1 kg.), and acidified with 2N-acetic acid (650 c.c.). The benzene layer was washed successively with 2N-acetic acid, water, 10% aqueous sodium carbonate, and water, then dried (Na_2SO_4) and evaporated. Distillation of the residue gave crude methyl αβ-epoxy-β-phenylpropionate (110 g.), b. p. 100—110°/0·6 mm., n_D^{15} 1·5333, which could not be further purified by distillation (Found: C, 64·5; H, 5·6. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%).

Methyl threo-α-*Hydroxy*-β-*phenyl*-β-*toluene*-p-*sulphonyloxypropionate*.—A solution of crude methyl αβ-epoxy-β-phenylpropionate (4·45 g.) and anhydrous toluene-*p*-sulphonic acid (4·7 g.) in dry ether (60 c.c.) was boiled under reflux for 15 min. and set aside at room temperature for 12 hours. The crystalline *ester* (3·5 g.) was washed with ether (20 c.c.) and recrystallised from carbon tetrachloride as colourless needles, m. p. 92°, which rapidly became brown on storage (Found: C, 57·7; H, 5·3; S, 9·1. $C_{17}H_{18}O_6S$ requires C, 58·3; H, 5·2; S, 9·2%). Treatment with toluene-*p*-sulphonyl chloride in pyridine afforded the *threo*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 132°. Acetylation (acetic anhydride in pyridine) afforded the threo-α-*acetate* β-*toluene*-p-*sulphonate* (needles), m. p. 83° (Found: C, 57·9; H, 5·2; S, 8·3. $C_{19}H_{20}O_7S$ requires C, 58·3; H, 5·1; S, 8·1%); treatment with methanesulphonyl chloride gave the threo-α-*methanesulphonate* β-*toluene*-p-*sulphonate* (needles), m. p. 111° (Found: C, 49·3; H, 4·7; S, 15·7. $C_{18}H_{20}O_8S_2$ requires C, 49·0; H, 4·7; S, 15·5%).

Reactions of the threo-αβ-*Diacyloxy*-β-*phenylpropionic Acids with Aqueous Alkali*.—(i) The diacetoxy-acid (4·0 g.) (Dieckmann, *Ber.*, 1910, **43**, 1035) with potassium hydroxide (14 g.) in water (50 c.c.) for 3 hours at 20° gave only *threo*-αβ-dihydroxy-β-phenylpropionic acid (1·95 g., 71%), m. p. and mixed m. p. 141°.

(ii) The dibenzoyloxy-acid (3·4 g.) (Mayer, *Ber.*, 1897, **30**, 1612) with potassium hydroxide (1·4 g.) in water (50 c.c.) for 12 hours at 20° gave only benzoic acid (0·97 g.) and the dihydroxy-acid (1·32 g., 83%), m. p. and mixed m. p. 141°.

Reactions of the Methyl threo-β-*Phenyl*-αβ-*disulphonyloxypropionates with Methanolic Alkali*.—(i) The ditoluene-*p*-sulphonate (10·9 g.) was shaken for 16 hours with potassium hydroxide (16·8 g.) in methanol (150 c.c.); the precipitated potassium toluene-*p*-sulphonate (8·4 g., 100%) was then removed. The solution was acidified with concentrated hydrochloric acid, and the precipitated potassium chloride filtered off and washed with methanol (10 c.c.). The combined filtrate and washings were diluted to 400 c.c. with water, concentrated under reduced pressure below 50° to 150 c.c., and extracted with ether (3 × 80 c.c.). Evaporation of the dried (Na_2SO_4) extracts gave a solid (3·9 g.), m. p. 165—170° (decomp.), which was freed from polymer by repeated precipitation with benzene from chloroform, to give fibrous filaments of "di(phenylpyruvic) acid," m. p. 172—173° (decomp.) (Found: C, 69·3; H, 4·6. Calc. for $C_{18}H_{14}O_6$: C, 69·7; H, 4·5%) (Jarrousse, *loc. cit.*, gives m. p. *ca.* 200°).

(ii) The dimethanesulphonate (7·4 g.), when similarly treated with potassium hydroxide (16·8 g.) in methanol (150 c.c.), gave potassium methanesulphonate (4·9 g.) and "di(phenylpyruvic) acid" (1·3 g.), m. p. 172—173° (decomp.).

Reactions of the Methyl β-*Phenyl*-αβ-*disulphonyloxypropionates with Aqueous Alkali*.—(i) The *threo*-ditoluene-*p*-sulphonate (10·1 g.) in dioxan (150 c.c.) was added to potassium hydroxide (6·8 g.) in water (50 c.c.), and the mixture shaken for 16 hours, diluted with water (150 c.c.), and neutralised with carbon dioxide. The dioxan was removed under reduced pressure, and the aqueous solution was extracted with ether (50 c.c.) to yield an oil (0·2 g.); on trituration with methanol this deposited a solid (0·13 g.) which crystallised from methanol in plates, m. p. 82°.

The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether (3 × 300 c.c.), to give α-*toluene*-p-*sulphonyloxycinnamic acid* (3·5 g.), m. p. 165° (from ethylene dichloride) (Found: C, 60·6; H, 4·7; S, 10·2. $C_{16}H_{14}O_5S$ requires C, 60·4; H, 4·4; S, 10·1%). Treatment of a portion with ethereal diazomethane afforded the *methyl* ester, which crystallised from methanol in plates, m. p. 83° (Found: C, 61·3; H, 5·0; S, 9·7. $C_{17}H_{16}O_5S$ requires C, 61·4; H, 4·9; S, 9·6%), identical with the solid obtained from the neutral fraction.

(ii) The *erythro*-ditoluene-*p*-sulphonate (5·0 g.) under the same conditions gave the same α-toluene-*p*-sulphonyloxycinnamic acid (1·6 g.), m. p. and mixed m. p. 165°; the methyl ester had m. p. and mixed m. p. 83°.

(iii) The *threo*-dimethanesulphonate (3·5 g.) in dioxan (75 c.c.), with potassium hydroxide (3·4 g.) in water (25 c.c.) similarly gave α-*methanesulphonyloxycinnamic acid* (1·9 g.), needles (from chloroform), m. p. 153° (Found: C, 49·2; H, 4·2; S, 13·3. $C_{10}H_{10}O_5S$ requires C, 49·6; H, 4·2; S, 13·2%). Treatment with diazomethane gave the *methyl* ester, m. p. 93° (from methanol) (Found: C, 51·6; H, 4·8; S, 12·8. $C_{11}H_{12}O_5S$ requires C, 51·6; H, 4·7; S, 12·5%).

(iv) The *erythro*-dimethanesulphonate (3·5 g.) gave the same α-methanesulphonyloxycinnamic acid (1·7 g.), m. p. and mixed m. p. 153°.

(v) Methyl *threo*-α-methanesulphonyloxy-β-phenyl-β-toluene-*p*-sulphonyloxypropionate (0·39 g.) in dioxan (7·5 c.c.), with potassium hydroxide (0·34 g.) in water (2·5 c.c.), afforded α-methanesulphonyloxycinnamic acid (0·21 g.), m. p. 141—144°; recrystallisation from chloroform gave needles, m. p. and mixed m. p. 153°. The methyl ester had m. p. and mixed m. p. 93°.

*Methyl α-Toluene-*p*-sulphonyloxycinnamate from Methyl β-Phenylpyruvate.*—β-Phenylpyruvic acid (0·82 g.), m. p. 150—154° (*Org. Synth.*, Coll. Vol. 2, p. 519) was treated with ethereal diazomethane, and the ester obtained on evaporation was dissolved in pyridine (10 c.c.) and cooled to −5°. Toluene-*p*-sulphonyl chloride (1·0 g.) was added, and after 16 hours at 0° the solution was diluted with ice-water (20 c.c.). The precipitated oil was extracted with chloroform (4 × 4 c.c.), washed with 20% aqueous sulphuric acid, then with water, and dried (Na_2SO_4). The solvent was evaporated, and the residual oil (0·5 g.) on trituration with methanol deposited a solid (0·19 g.), m. p. 74—78°; recrystallisation from methanol afforded methyl α-toluene-*p*-sulphonyloxycinnamate, m. p. and mixed m. p. 82°.

Reactions of α-Sulphonyloxycinnamic Acids with Aqueous Alkali.—α-Toluene-*p*-sulphonyloxycinnamic acid (0·2 g.) was boiled under reflux for 1 hour with potassium hydroxide (0·18 g.) in water (10 c.c.), and the cooled solution was acidified with hydrochloric acid and extracted with ether (3 × 5 c.c.), to give a solid (0·1 g.), m. p. 120—131°. Recrystallisation from chloroform afforded phenylpyruvic acid, m. p. 145°.

α-Methanesulphonyloxycinnamic acid (0·26 g.), similarly treated, gave phenylpyruvic acid (0·14 g.), m. p. 146°.

*Reactions of the αβ-Dimethanesulphonyloxy-esters with Sodium Iodide.**—(i) Methyl *threo*-αβ-dimethanesulphonyloxy-β-phenylpropionate (2·54 g.) and sodium iodide dihydrate (5·0 g.) in acetone (300 c.c.) were refluxed for 49 hours; the precipitated double salt of sodium methanesulphonate and sodium iodide (1·21 g.) was removed and the filtrate evaporated under reduced pressure. Water (20 c.c.) and chloroform (100 c.c.) were added, the iodine was removed by means of a saturated solution of sodium thiosulphate, and the chloroform layer separated, dried (Na_2SO_4), and evaporated. The semi-solid residue was dissolved in methanol (4 c.c.), then cooled, and the unchanged dimethanesulphonate which crystallised (0·83 g.) was filtered off; addition of light petroleum (b. p. 40—60°) to the filtrate precipitated a further quantity (0·12 g.). The filtrate was evaporated, water (35 c.c.) added, and the mixture distilled in steam. The steam-volatile methyl cinnamate (0·45 g.) was collected and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 36°.

(ii) Methyl *erythro*-αβ-dimethanesulphonyloxy-β-phenylpropionate (2·0 g.) and sodium iodide dihydrate (4 g.) in acetone (50 c.c.) when refluxed for 34 hours gave the sodium methanesulphonate–sodium iodide double salt (1·3 g.) and a steam-volatile ester (0·54 g.), b. p. 124—125°/16 mm. This was identified as methyl *cis*-cinnamate by *cis*-hydroxylation, and by hydrolysis, as follows: The ester (0·3 g.) in ethanol (20 c.c.) at −30° was treated with potassium permanganate (0·35 g.) and magnesium sulphate heptahydrate (0·35 g.) in water (11 c.c.) and gave methyl *erythro*-αβ-dihydroxy-β-phenylpropionate (0·14 g.), m. p. and mixed m. p. 87°. The unsaturated ester (0·2 g.) when hydrolysed gave *cis*-cinnamic acid (0·13 g.), m. p. 42°.

(iii) Methyl *erythro*-αβ-dimethanesulphonyloxybutyrate (2·0 g.) and sodium iodide dihydrate (4·0 g.) in acetone (50 c.c.) were refluxed for 28 hours; the double salt (1·82 g.) was filtered off and the filtrate evaporated under reduced pressure. Water (2 c.c.) and a saturated solution of sodium thiosulphate (3 c.c.) were added, the mixture was extracted with ether (4 × 6 c.c.), and the extract dried (Na_2SO_4) and evaporated. The residue (0·4 g.) was hydrolysed at room temperature with aqueous alcoholic (1 : 1) 0·5N-potassium hydroxide (10 c.c.) and gave a liquid unsaturated acid, b. p. 169° (0·1 g.) (*cis*-crotonic acid has b. p. 169°). This was re-esterified and treated with methanolic ammonia for several days at 0°. Evaporation, and recrystallisation of the residue from water, gave *cis*-crotonamide, m. p. 100—101° (lit., 102°), depressed to 94—97° on admixture with *trans*-crotonamide.

(iv) Methyl *threo*-αβ-dimethanesulphonyloxybutyrate (2·0 g.) when refluxed with sodium iodide dihydrate (4·0 g.) in acetone (50 c.c.) gave an ester (0·4 g.), b. p. 116°, which on hydrolysis afforded *trans*-crotonic acid (0·2 g.), m. p. and mixed m. p. 73°.

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* These reactions were carried out with exclusion of light.

245. *Elimination Reactions of Esters. Part III.* Derivatives of Dibasic Polyhydroxy-acids.*

By R. P. Linstead, L. N. Owen, and R. F. Webb.

The diacetate and the dimethanesulphonate of dimethyl (±)-ββ′-dihydroxyadipate undergo elimination with alkali and give *trans-trans*-muconic acid. Dimethyl mucate, with methanesulphonyl chloride and pyridine, undergoes esterification and elimination to give dimethyl *trans-trans*-αα′-dimethanesulphonyloxymuconate. Complicated changes occur on treatment of dimethyl **2 : 3 : 4 : 5**-tetra-*O*-acetylmucate with dilute alkali; one product is αα′-dihydroxymuconic acid (αα′-diketoadipic acid).

Hydroxylation of *trans*-Δ^{β}-dihydromuconic acid with pertungstic acid results in a considerable amount of *cis*-addition, and gives the dilactone of (±)-ββ′-dihydroxyadipic acid. This, in cold alkaline solution, isomerises to the unsaturated lactonic acid, γ-carboxymethyl-Δ^{α}-butenolide. Mannosaccharodilactone, known to undergo a similar change under mild conditions (Heslop and F. Smith, *J.*, 1944, 577), on more vigorous treatment gives some αα′-dihydroxymuconic acid.

Only one ester group in the 2 : 5-dimethanesulphonate of mannosaccharodilactone is removed by reaction with sodium iodide and the product is probably γ-carboxymethylene-α-methanesulphonyloxy-Δ^{α}-butenolide; a stereoisomer is formed in a similar reaction with calcium carbonate.

The stereochemical results of these reactions can be explained by a mechanism of *trans*-elimination in all cases.

The elimination reactions described in Parts I and II (preceding papers) involved derivatives of mono- and di-hydroxy-monocarboxylic acids. In extending the investigation to dicarboxylic acids, some derivatives of ββ′-dihydroxyadipic acid were studied first, because they were expected to give a muconic acid, the various stereoisomers of which are now well known (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235).

cis-Hydroxylation of methyl *trans*-Δ^{β}-dihydromuconate (I) with buffered aqueous permanganate at low temperature gave crystalline dimethyl (±)-ββ′-dihydroxyadipate (II), from which the diacetate and ditoluene-*p*-sulphonate (VIII) were prepared; with cold potassium hydroxide in aqueous dioxan both derivatives underwent a double elimination reaction and gave *trans-trans*-muconic acid (VII). In these reactions the probable occurrence of *trans*-elimination at each position in no way controls the stereochemistry of the resulting muconic acid, because two hydrogen atoms are available at each α-position, and free rotation is possible between all the carbon atoms in the saturated compounds. The formation of the *trans-trans*-acid is a consequence only of the fact that it is the most stable of the three isomers.

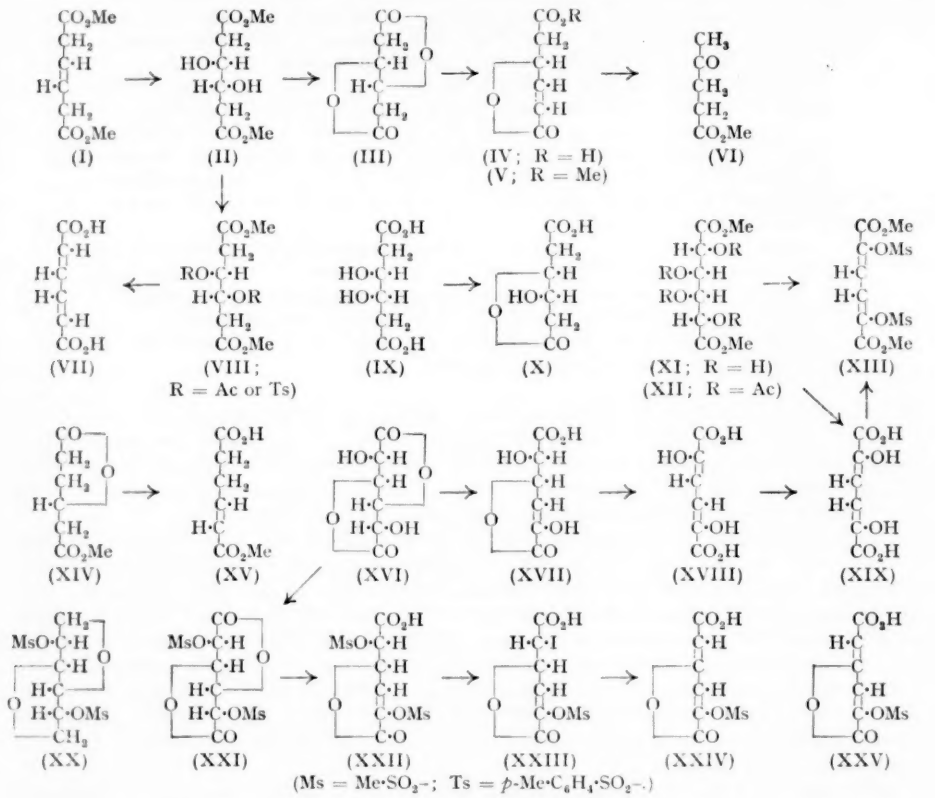
Attempts to prepare *meso*-ββ′-dihydroxyadipic acid (IX) by *trans*-hydroxylation of *trans*-Δ^{β}-dihydromuconic acid were unsuccessful. With pertungstic acid, a reagent which is stated (Mugdan and Young, *J.*, 1949, 2999) to bring about *trans*-addition, the product was a mixture of a mono- and a di-lactone, the latter being identical with the compound (III) previously isolated from the lactonisation products of *cis-cis*-muconic acid (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228; Elvidge, Linstead, Sims, and Orkin, *loc. cit.*). By analogy with the corresponding carbon-ring compounds (Barrett and Linstead, *J.*, 1935, 436) a *cis*-fusion of the two five membered rings is favoured, and the dilactone is therefore derived from the (±)-acid and not from the *meso*-form; † this is supported by the observation that the dilactone is obtained in almost quantitative yield by acid hydrolysis of the (±)-ester (II). The *meso*-acid, however, could form a monolactone (X), and it seems therefore, from the isolation of both products, that pertungstic acid has given both *cis*- and *trans*-hydroxylation. Reaction of *trans*-Δ^{β}-dihydromuconic

* Part II, preceding paper.

† Compare the ready formation of dilactones from mannosaccharic and glucosaccharic acids (*trans*-configuration of hydroxyls at $C_{(3)}$ and $C_{(4)}$), but not from mucic acid (*cis*-configuration).

acid with performic acid, a reagent which invariably results in *trans*-hydroxylation, gave only the monolactone (X); no dilactone could be detected.

Treatment of the methyl ester of (X) with toluene-*p*-sulphonyl chloride and pyridine gave γ-(methoxycarbonylmethyl)-Δ^{α}-butenolide (V); this reaction probably proceeds through the intermediate β-toluene-*p*-sulphonate, which is so unstable that it undergoes elimination of acid in the presence of pyridine. A similar reaction was shown by dimethyl mucate (XI), which on treatment with methanesulphonyl chloride and pyridine gave dimethyl *trans-trans*-αα′-dimethanesulphonyloxymuconate (XIII); the corresponding



ditoluene-*p*-sulphonate was obtained in the same way. Presumably the tetrasulphonates are initially formed, but are spontaneously decomposed by the pyridine. The configuration assigned to (XIII) is based on the assumption that *trans*-elimination occurs from both the β-positions; the presence of the highly conjugated muconic acid structure was confirmed by the absorption spectrum (maxima at 2720 and 2800 Å, ε 16,000 and 18,000). Unlike the α-sulphonyloxy-derivatives of crotonic and cinnamic acids, which were readily hydrolysed to the α-keto-acids (Part II, *loc. cit.*), the methanesulphonate (XIII) and the corresponding toluene-*p*-sulphonate were comparatively resistant; prolonged boiling with alkali, with a view to obtaining αα′-dihydroxymuconic acid (αα′-diketoadipic acid) gave only tars.

Kremann (*Monatsh.*, 1905, **26**, 783) found that hydrolysis of diethyl mucate and of tetra-*O*-acetylmucic acid with alcoholic alkali proceeded normally and gave a colourless solution, whereas diethyl tetra-*O*-acetylmucate gave a yellow solution and a brown precipitate which, although consisting largely of sodium mucate, contained an unidentified by-product. Simon and Guillaumin (*Compt. rend.*, 1924, **179**, 1324) reported, however,

that dimethyl tetra-*O*-acetylmucate (XII) on alkaline hydrolysis gave a quantitative yield of potassium mucate, though no experimental details were given. We found that this ester (XII), on brief treatment with an excess of warm aqueous-alcoholic alkali, gives a yellow solution having light-absorption consistent with the formation of αα′-dihydroxymuconic acid (XIX) (cf. Haworth, Hirst, and Jones, *J.*, 1938, 710; Wille, *Annalen*, 1939, **538**, 237). When the alkaline solution was kept for a short time the absorption spectrum altered, probably owing to further changes involving cyclisation to an α-pyrone, and ketonisation to αα′-diketoadipic acid; confirmation of the formation of the diketo-acid was provided by oxidation to succinic acid. Tetra-*O*-acetylmucic acid on similar treatment gave a colourless solution with no appreciable light-absorption, which shows that the activating effect of the free carboxyl groups is insufficient to cause elimination of acid. In Part I (*loc. cit.*) it was shown that elimination is favoured by the production of a highly conjugated product, and this probably accounts for the occurrence of elimination with (XII) and not with methyl αβ-diacetoxybutyrate (Part II, *loc. cit.*).

It has been pointed out (Elvidge, Linstead, *et al.*, *locc. cit.*) that the alkaline isomerisation of certain lactones to unsaturated acids is a special case of the elimination of a β-acyl group to form an αβ-double bond. Thus the lactone (XIV), which is an intramolecularly acylated β-hydroxy-ester, with sodium methoxide gives the αβ-unsaturated ester (XV). It was therefore of interest to examine the behaviour of the dilactone (III) towards alkali. The compound in aqueous solution showed no appreciable light absorption above 2200 Å, but in alkaline solution it showed end-absorption (ε 1200 at 2260 Å) which persisted, though with lower intensity (ε 400 at 2260 Å), when the solution was acidified. This behaviour suggested that isomerisation had occurred into the unsaturated lactonic acid (IV) (which also showed end-absorption of intensity greater in alkaline than in acid solution), and this was confirmed by isolation of (IV) after momentary treatment of the dilactone with 1 equivalent of cold dilute sodium hydroxide solution. A closely related compound, D-mannosaccharo-1 → 4 : 6 → 3-dilactone (XVI), has been shown by F. Smith and his associates to be very readily isomerised under mild conditions. Thus, with cold methanolic sodium methoxide it gives the enolic lactonic acid (XVII) (Heslop and Smith, *J.*, 1944, 577) whilst with diazomethane, or with silver oxide and methyl iodide, the corresponding methylated product is obtained (Haworth, Heslop, Salt, and Smith, *ibid.*, p. 217). The formation of (XVII) from (XVI) is exactly analogous to the conversion of the dilactone (III) into the lactonic acid (IV), and it is significant that the configuration of (XVI) is such that *trans*-elimination between $C_{(4)}$ and $C_{(5)}$ would give the necessary *cis*-configuration at the double bond in (XVII). We have now found that when mannosaccharodilactone is treated with an excess of sodium methoxide both lactone rings are opened to give an αα′-dihydroxymuconic acid, which, on the assumption that the second elimination also proceeds by a *trans*-mechanism, would be expected to have the *cis-cis*-configuration (XVIII). Since, however, the product is a di-enol, there is little doubt that under the basic conditions it would isomerise, through the diketo-form, into the more stable *trans-trans*-structure (XIX); its properties were, in fact, similar to those described by Wille (*loc. cit.*) for the αα′-dihydroxymuconic acid obtained by enolisation of αα′-diketoadipic acid, and its dimethyl ester, with methanesulphonyl chloride and pyridine, gave the dimethanesulphonate (XIII). The dilactone (III) might be expected to undergo a similar double elimination reaction with excess of alkali, but it has already been shown (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*) that the lactonic acid (IV) with hot aqueous sodium hydroxide gives lævulic acid, and not muconic acid; consequently it was not unexpected to find that methyl lævulate (VI) was obtained when the dilactone (III) was treated with an excess of hot methanolic sodium methoxide. The formation of keto-ester clearly involves a base-catalysed migration of the double bond in (IV), possibly after opening of the lactone ring, which evidently occurs much more readily than in (XVII).

Treatment of mannosaccharodilactone with methanesulphonyl chloride, toluene-*p*-sulphonyl chloride, or thionyl chloride under a variety of conditions gave only tars, but with methanesulphonic anhydride an almost quantitative yield of the crystalline 2 : 5-dimethanesulphonate (XXI) was obtained. This reacted with sodium iodide in boiling acetone, but only one sulphonyloxy-group was attacked. Since positions 2 and 5 in the

manno-configuration are identical, this result is at first sight very surprising, particularly since Wiggins and Wood (*J.*, 1951, 1180) have found that both ester groups in 2 : 5-dimethanesulphonyl 1 : 4-3 : 6-dianhydromannitol (XX) are reactive towards sodium iodide. In the present instance, however, a crystalline product, m. p. 155—156°, isolated in fair yield, had the properties and equivalent weight of an unsaturated monocarboxylic lactone; the absorption spectrum was similar to that of γ-carboxymethylene-Δ^{α}-butenolide (cf. Eisner, Elvidge, and Linstead, *J.*, 1951, 1501) and the compound is therefore formulated as γ-carboxymethylene-α-methanesulphonyloxy-Δ^{α}-butenolide (XXIV). If it be assumed that the initial reaction is an isomerisation of (XXI) to (XXII), the sulphonyloxy-group at $C_{(5)}$ would be expected, from analogy with (XIII), to be comparatively resistant. Under vigorous conditions (*e.g.*, at 120° under pressure) this remaining group was attacked by sodium iodide, lithium chloride, or potassium thiolacetate, but no recognisable products could be isolated.

When (XXI) was treated with calcium carbonate in boiling aqueous acetone it gave a compound, m. p. 144—145°, isomeric with (XXIV) and showing almost identical light-absorption, but the mixed melting point showed marked depression. The two products may be stereoisomers with regard to the exocyclic double bond; an initial replacement of the reactive methanesulphonyloxy-group by iodine, with inversion, to give (XXIII), followed by *trans*-elimination of hydrogen iodide, would clearly result in a *trans*-configuration (XXIV), whereas direct *trans*-elimination of methanesulphonic acid from (XXII) would give the *cis*-configuration (XXV).

Experimental

Dimethyl trans-Δ^{β}-*Dihydromuconate*.—Esterification (methanol–sulphuric acid) of *trans*-Δ^{β}-dihydromuconic acid (Ahmad, Sondheimer, Weedon, and Woods, *J.*, 1952, 4089) gave the dimethyl ester, b. p. 82°/0·2 mm., n_D^{21} 1·4490.

Dimethyl (±)-ββ′-*Dihydroxyadipate*.—To a vigorously stirred solution of *trans*-Δ^{β}-dihydromuconate (2·65 g.) in ethanol (100 c.c.), cooled to −40°, a solution of potassium permanganate (3·0 g.) and magnesium sulphate heptahydrate (3·0 g.) in water (100 c.c.) was added during 4 hours. The mixture was set aside at room temperature for 12 hours and then filtered, the manganese dioxide being thoroughly washed with water. The combined filtrate and washings were concentrated under reduced pressure and continuously extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave a solid (0·9 g.) which on crystallisation from carbon tetrachloride afforded *dimethyl* (±)-ββ′-*dihydroxyadipate*, m. p. 76—77° (Found: C, 46·6; H, 7·1. $C_8H_{14}O_6$ requires C, 46·6; H, 6·9%). The *diacetate* (acetic anhydride–pyridine) formed needles (from carbon tetrachloride), m. p. 78°, b. p. 114—115°/0·001 mm. (Found: C, 49·7; H, 6·5. $C_{12}H_{18}O_8$ requires C, 49·6; H, 6·3%), and the *ditoluene*-p-*sulphonate* (toluene-*p*-sulphonyl chloride–pyridine at 0°), needles (from methanol), m. p. 142—143° (Found: C, 51·7; H, 5·5; S, 12·3. $C_{22}H_{26}O_{10}S_2$ requires C, 51·3; H, 5·1; S, 12·5%).

Action of Alkali on the (±)-*Diacetoxy- and Ditoluene*-p-*sulphonyloxy-adipates*.—(i) The diacetate (0·6 g.) was stirred at room temperature for 16 hours with potassium hydroxide (0·7 g.) in water (5 c.c.) and dioxan (13 c.c.); the excess of alkali was then neutralised with hydrochloric acid, and the dioxan was removed under reduced pressure with occasional addition of water. The solution was acidified with hydrochloric acid, concentrated (to 25 c.c.) at 40°/14 mm., and cooled. The precipitated solid (0·12 g.), m. p. 296—299°, was dissolved in aqueous sodium hydrogen carbonate; acidification of the filtered solution gave *trans-trans*-muconic acid, m. p. and mixed m. p. 300—301°.

(ii) The ditoluene-*p*-sulphonate (2·6 g.) was stirred for 12 hours with potassium hydroxide (3·4 g.) in water (25 c.c.) and dioxan (75 c.c.); the *trans-trans*-muconic acid (0·6 g.), isolated as above, had m. p. and mixed m. p. 301°.

γγ-*Dilactone of* (±)-ββ′-*Dihydroxyadipic Acid*.—A solution of dimethyl (±)-ββ′-dihydroxyadipate (30 mg.) in N-hydrochloric acid (5 c.c.) was slowly evaporated on the steam-bath (1 hour). The residue (20 mg.) solidified, and on crystallisation from ethyl acetate gave the dilactone, m. p. 127—128°, not depressed by a sample of similar m. p. prepared from *cis-cis*-muconic acid (Elvidge, Linstead, Orkin, *et al.*, *loc. cit.*).

Attempted trans-*Hydroxylation of* trans-Δ^{β}-*Dihydromuconic Acid*.—(i) Tungstic oxide (40 mg.) was dissolved in 30% hydrogen peroxide (35 c.c.) and water (50 c.c.); Δ^{β}-dihydromuconic acid (25·2 g.) in water (50 c.c.) was added, and the solution was stirred at 70° for 6 hours. Excess

of hydrogen peroxide was destroyed with sodium hydrogen sulphite (*ca.* 0·5 g.), and the solution acidified with 2N-hydrochloric acid and evaporated under reduced pressure. The residual dark syrup was extracted with acetone, and the extract dried ($MgSO_4$) and evaporated to a syrup (18 g.) which was dissolved in hot ethyl acetate (20 c.c.); from the cooled solution crystals (8·2 g.), m. p. 123—125°, were deposited. Recrystallisation from ethyl acetate afforded the $\gamma\gamma$-dilactone, m. p. and mixed m. p. 127—128°, of (±)-ββ′-dihydroxyadipic acid. The original mother-liquors, after concentration, slowly deposited an acidic solid (4·3 g.), m. p. 53—62°. Recrystallisation from ethyl acetate gave hard nodules of *γ-carboxymethyl-β-hydroxybutanolide* (*γ-lactone* of *meso*-ββ′-dihydroxyadipic acid) (X), m. p. 91° (Found: C, 45·0; H, 5·2. $C_6H_8O_5$ requires C, 44·9; H, 5·1%).

(ii) [With P. Sims.] *trans*-Δ^{β}-Dihydromuconic acid (1 g.), formic acid (10 c.c.), and 30% hydrogen peroxide (0·9 c.c.) were kept together at 45° for an hour and then steam-distilled. The aqueous residue was evaporated under reduced pressure to a syrup, which slowly deposited a solid (0·6 g.). Recrystallisation from ethyl acetate gave the above monolactone, m. p. and mixed m. p. 91—92°.

γ-(Methoxycarbonylmethyl)-Δ^{α}*-butenolide.*—Treatment of γ-carboxymethyl-β-hydroxybutanolide (0·5 g.) with ethereal diazomethane furnished the viscous methyl ester (0·5 g.), b. p. 125°/0·0001 mm., which was dissolved in pyridine (1·5 c.c.), cooled to 0°, and treated with toluene-*p*-sulphonyl chloride (0·67 g.). After 60 hours at 0°, the mixture was diluted with ice-water (10 c.c.) and extracted with chloroform. The extracts were washed with 2N-sulphuric acid and with water, dried (Na_2SO_4), and distilled, to give a sulphur-free oil (0·3 g.), b. p. 82°/0·001 mm., n_D^{23} 1·4715. This failed to crystallise (Elvidge, Linstead, Orkin, *et al.*, *loc. cit.*, give m. p. 31°), but treatment of γ-carboxymethyl-Δ^{α}-butenolide with ethereal diazomethane, and distillation in the apparatus previously used, gave an identical product, b. p. 82°/0·001 mm., n_D^{23} 1·4718.

Dimethyl trans-trans-αα′*-Dimethanesulphonyloxymuconate.*—To dimethyl mucate (1·2 g.) suspended in pyridine (20 c.c.) at −5°, methanesulphonyl chloride (3·0 g.) in pyridine (10 c.c.) was added during ½ hour. The mixture was set aside at 0° for 20 hours, and diluted with ice-water (80 c.c.); the precipitate (1·3 g.) crystallised from di*iso*propyl ketone in colourless needles of *dimethyl* trans-trans-αα′*-dimethanesulphonyloxymuconate*, m. p. 204° (Found: C, 33·9; H, 4·3; S, 18·1. $C_{10}H_{14}O_{10}S_2$ requires C, 33·5; H, 3·9; S, 17·9%). Light absorption in dioxan: max. 2720, 2800 Å; ε 16,100, 18,300.

Dimethyl trans-trans-αα′*-Ditoluene-*p*-sulphonyloxymuconate.*—Similar treatment of dimethyl mucate (1·2 g.) in pyridine (20 c.c.) with toluene-*p*-sulphonyl chloride (4·1 g.) for 16 hours at 0° and 48 hours at room temperature gave plates (1·6 g.) (from chloroform–alcohol) of *dimethyl* trans-trans-αα′*-ditoluene-*p*-sulphonyloxymuconate*, m. p. 196° (Found: C, 51·4; H, 4·5; S, 12·2. $C_{22}H_{22}O_{10}S_2$ requires C, 51·7; H, 4·3; S, 12·5%).

Reactions of the Dilactone (III).—(a) *With aqueous sodium hydroxide.* (i) The dilactone (8 mg.) was dissolved in 0·05N-sodium hydroxide (10 c.c.). The solution gradually became bright yellow (5 minutes) and showed end light-absorption (ε 1200 at 2260 Å) which persisted (ε 400 at 2260 Å) in the colourless solution obtained when a portion was acidified with hydrochloric acid. When kept, the original alkaline solution became much paler, and after ½ hour was almost colourless, but there was little change in light-absorption (ε 1100 at 2260 Å; ε 400 after acidification). Similar colour changes occur with the γ-lactone of β-methylglucofuranoside (Owen, Peat, and Jones, *J.*, 1941, 339), which also contains two five-membered rings.

(ii) 1·00N-Sodium hydroxide (0·75 c.c.) was added to the dilactone (80 mg.) in water (2 c.c.). After 1 minute, 1·00N-hydrochloric acid (0·75 c.c.) was added, and the solution was evaporated to dryness at 0·2 mm. in a vacuum-desiccator over calcium chloride. The residue was triturated with ether (3 × 2 c.c.), which on evaporation gave a solid (30 mg.); recrystallisation from ethanol–benzene afforded γ-carboxymethyl-Δ^{α}-butenolide, m. p. and mixed m. p. 110°, which showed end light-absorption (at 2260 Å, ε 3100 in 0·05N-sodium hydroxide; ε 1400 after acidification).

(b) *With methanolic sodium methoxide.* The dilactone (2·3 g.) was kept with 0·2N-methanolic sodium methoxide (82 c.c.) at room temperature for 48 hours. Water (4 c.c.) was added, and the solution was neutralised with carbon dioxide, freed from methanol by evaporation, diluted with water (40 c.c.) and 2N-hydrochloric acid (12 c.c.), and continuously extracted with ether to give methyl lævulate (0·5 g.), b. p. 32°/0·0001 mm., n_D^{18} 1·4215 (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 140°).

Alkaline Hydrolysis of Dimethyl 2 : 3 : 4 : 5*-Tetra-*O*-acetylmucate.*—(i) To the ester (6 mg.)

(Simon and Guillaumin, *loc. cit.*) in ethanol (5 c.c.) at 60°, 2N-sodium hydroxide (0·1 c.c.) was added. The solution became bright yellow and cloudy. After 1 minute it was cooled and diluted to 10 c.c. with water, a clear yellow solution being obtained. This showed maximum light-absorption at 2650 and 3650 Å (ε 5000), changing on acidification (colourless solution) to 3230 Å (ε 5000). When the original alkaline solution was kept for an hour it became paler and showed maxima at 2930 and 3040 Å (ε *ca.* 1000), but the original acidified solution showed no change in appearance or absorption.

(ii) 2N-Sodium hydroxide (5 c.c.) was added to the ester (0·4 g.) in hot ethanol (20 c.c.). After 2 minutes, water (20 c.c.) was added and the clear yellow solution was cooled, acidified with 2N-sulphuric acid (10 c.c.), and concentrated under reduced pressure, with gradual addition of water, to remove all alcohol. More 2N-sulphuric acid (20 c.c.) was added, and the solution was heated to 70° and treated with 2% aqueous potassium permanganate until a pink colour persisted for 5 minutes. A trace of sodium sulphite was added to decolourise the filtered solution, which was then neutralised with sodium hydroxide, acidified with hydrochloric acid, and evaporated to dryness under reduced pressure. Extraction of the residue with boiling acetone gave an oil (0·1 g.) which partly crystallised and gave a strong fluorescein test with resorcinol and sulphuric acid; purification of the solid by sublimation and by recrystallisation from water gave succinic acid, m. p. 184°.

*Mannosaccharo-*1→4 : 6→3-*dilactone.*—Mannitol (60 g.) was heated at 60° with concentrated nitric acid (170 c.c.) and water (40 c.c.). After about 15 minutes the oxidation became vigorous and the solution was cooled in ice. It was then heated for 4 hours at 60° and for ½ hour at 85°, and evaporated under reduced pressure to a syrup, which was dissolved in ethanol (20 c.c.), and treated with ether (500 c.c.). The precipitate was recrystallised from 1 : 1 ethanol–ether (160 c.c.), and finally from ethanol, to give mannosaccharo-1→4 : 6→3-dilactone (12 g.), m. p. 187°, $[\alpha]_D^{22}$ +204° (*c*, 1·0 in water).

*Reaction of Mannosaccharo-*1→4 : 6→3-*dilactone with Sodium Methoxide.*—Sodium (4·6 g.) was dissolved in dry methanol (550 c.c.), the dilactone (4 g.) and glass beads were added, and the solution was refluxed under nitrogen for 6 hours. The orange precipitate (4·9 g.) was washed with ether and dissolved in water (100 c.c.). The solution was acidified with hydrochloric acid and evaporated at 40°/14 mm., under nitrogen, and the residue (dried by storage *in vacuo* over phosphoric oxide) extracted with dioxan (4 × 50 c.c.). The extracts, concentrated to 20 c.c., slowly deposited a solid (0·33 g.), m. p. 198—204°. Recrystallisation from dioxan afforded *trans-trans-*αα′-dihydroxymuconic acid, m. p. 242° (Wille, *loc. cit.*, gives m. p. 226—227° for the di-enol, and 234° for the diketo-acid). Treatment of a portion (0·1 g.) with boiling 1% methanolic hydrogen chloride gave the dimethyl ester (0·06 g.), m. p. 166° (from dioxan) (Wille, *loc. cit.*, gives m. p. 169—170°); light absorption in dioxan: max. 3230 Å, ε 14,800. With methanesulphonyl chloride and pyridine, this ester gave dimethyl αα′-dimethanesulphonyloxymuconate, m. p. 196—197°, not depressed on admixture with the compound, m. p. 204°, prepared from dimethyl mucate.

2 : 5-*Dimethanesulphonyl Mannosaccharo-*1→4 : 6→3-*dilactone.*—The mannosaccharodilactone (1·25 g.) was dissolved in methanesulphonic anhydride (5·0 g.) (Billeter, *Ber.*, 1905, **38**, 2018) by gentle warming; one drop of sulphuric acid was added and the solution was heated at 70° until it solidified (10 minutes). The product was cooled, water (40 c.c.) added, and the precipitated solid (2·4 g.), m. p. 176—179°, was washed with water and crystallised from ethyl formate in silky needles of 2 : 5-*dimethanesulphonyl mannosaccharo-*1→4 : 6→3-*dilactone*, m. p. 200—201°, $[\alpha]_D^{20}$ +151° (*c*, 2 in dioxan) (Found: C, 29·3; H, 3·1; S, 19·4. $C_8H_{10}O_{10}S_2$ requires C, 29·1; H, 3·1; S, 19·4%).

Reactions of 2 : 5-*Dimethanesulphonyl Mannosaccharo-*1→4 : 6→3-*dilactone.*—(i) A solution of the dimethanesulphonate (6·6 g.) and sodium iodide dihydrate (15 g.) in acetone (200 c.c.) was refluxed, with occasional filtration, until 1 mol. (3·2 g.) of the sodium methanesulphonate–sodium iodide double salt had been precipitated (4 hours). The acetone was removed under reduced pressure, and the residue stirred with water (40 c.c.) and sufficient sodium thiosulphate to remove free iodine. Extraction with ether gave a solid, which on crystallisation from ethylene dichloride gave needles (3·8 g.) of *γ-carboxymethylene-α-methanesulphonyloxy-*Δ^{α}-*butenolide*, m. p. 155—156° (Found: C, 36·1; H, 2·6; S, 13·6%; equiv. by rapid titration with 0·05N-baryta, 217. $C_7H_8O_7S$ requires C, 35·9; H, 2·6; S, 13·7%; equiv., 234). Light absorption in dioxan: max. 2510, 2690, 2800 Å; ε 10,500, 14,000, 16,800. With ethereal diazomethane it gave needles (from methanol) of *α-methanesulphonyloxy-γ-(methoxycarbonylmethylene)-*Δ^{α}-*butenolide*, m. p. 111—112° (Found: C, 39·1; H, 3·4. $C_8H_8O_7S$ requires C, 38·7; H, 3·25%).

(ii) The dimethanesulphonate (5 g.), calcium carbonate (12 g.), water (5 c.c.), and acetone (150 c.c.) were refluxed for 24 hours; solid was then removed and washed with acetone (50 c.c.). The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure; the residue (2·5 g.), m. p. 138—140°, on recrystallisation from ethylene dichloride afforded an isomeric *γ-carboxymethylene-α-methanesulphonyloxy-*Δ^{α}*-butenolide*, m. p. 144—145° (Found: C, 36·1; H, 2·85; S, 13·6%; equiv., 212); light absorption in dioxan: max. 2510, 2690, 2800 Å; ε 9400, 14,500, 18,800. The m. p. was depressed to 137—139° on admixture with the isomer of m. p. 155—156°.

Light absorptions were determined in the spectrographic laboratory of this Department (Mrs. A. I. Boston).

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246. *Thermal Mutarotation of Some Methylated* D-*Fructoses.*

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The equilibrium $[\alpha]_D$ in water of methylated fructoses is noticeably affected by temperature. Use of this optical measurement to characterise these sugars therefore demands careful temperature control. A structural factor common to the sugars known to show this thermal mutarotation is noted. The symbol $[^{t_1}\Delta^{t_2}]_D$ is proposed to denote the change in equilibrium $[\alpha]_D$ for a *rise* of 1° c measured between the two temperatures $t_1°$ and $t_2°$.

More than one hundred years ago it was observed that the optical rotation of sugars is affected by temperature; towards the end of the nineteenth century it was found that certain monosaccharides show much greater variations of equilibrium $[\alpha]_D$ with change of temperature than do others (cf. Browne and Zerban, "Sugar Analysis," John Wiley & Sons, New York, 1941, 3rd Edn., pp. 270 *et seq.*). This phenomenon, termed "thermal mutarotation" by Isbell and Pigman (*J. Res. Nat. Bur. Stand.*, 1938, **20**, 773), does not appear to have attracted much attention among academic carbohydrate chemists.

During examination of several specimens of analytically and chromatographically pure crystalline 1 : 3 : 4-trimethyl D-fructose apparent variations in $[\alpha]_D$ were traced to thermal mutarotation which in this substance is more marked than in any other sugar. Other chromatographically pure methylated D-fructoses available in this laboratory likewise show thermal mutarotation (Table 1). It is proposed that the change in equilibrium $[\alpha]_D$ (in water) produced by a *rise* in temperature of 1° c and observed between temperatures $t_1°$ and $t_2°$ shall be denoted by $[^{t_1}\Delta^{t_2}]_D$.

Table 1.

D-Fructose derivative:	1-Me	3-Me	1 : 3 : 4-Me_3	1 : 3 : 4 : 5-Me_4	3 : 4 : 6-Me_3	1 : 3 : 4 : 6-Me_4
$[\alpha]_D^{20\cdot0}$	−63·3°	−61·3°	−55·7°	−122°	+29·5°	+30·3°
$[^5\Delta^{30}]_D$	+0·450	+0·700	+0·820	+0·112	−0·130 *	−0·169

* Isbell and Pigman (*loc. cit.*) found −0·132.

Sugars which can undergo the pyranose ⇌ furanose change show markedly greater $[\Delta]_D$ when compared with the "fixed" derivatives able to exist in only one ring-form. If keto-sugars and their hydrates are assumed to be absent, the thermal mutarotation of the "fixed" sugars must be almost entirely due to a change in the anomeric equilibria. (A small proportion of the numerical change must be ascribed to such physical effects as alteration of indices of refraction, etc.) It therefore seems probable that the sugars able to assume different ring-forms will owe part of their thermal mutarotation to anomeric interchanges (cf. Isbell and Pigman, *loc. cit.*).

The monosaccharides, and their derivatives, which show thermal mutarotation have a property in common. Table 2 records the known data for dilute (2—8%) solutions. Each of these sugars possesses the *arabo*-configuration with respect to the ring carrying the

TABLE 2.

Sugar	$[\Delta]_D$	References
L-Arabinose	−0·394	Tanret, *Bull. Soc. chim.*, 1896, **15**, 195.
D-Galactose	−0·209	Meissl, *J. pr. Chem.*, 1880, **22**, 97.
D-Fructose	+0·580	Vosburgh, *J. Amer. Chem. Soc.*, 1920, **42**, 1696.
	+0·552	Tsuzuki *et al.*, *ibid.*, 1950, **72**, 1071.
	+0·549	Isbell and Pigman, *loc. cit.*
3 (α-D-Glucopyranosyl)-D-fructose (turanose)	+0·549	*Idem*, *ibid.*
4-(β-D-Galactopyranosyl)-D-fructose (lactulose)	+0·296	*Idem*, *ibid.*

reducing group and undergoes an identical stereoisometric change with the pyranose ⇌ furanose interconversion (disregarding D- and L-enantiomorphism). The furanose ring has a more symmetrical configuration with respect to the distribution of radicals above and below its plane :

Sugars which possess a symmetrical arrangement of radicals about the *pyranose* ring, *e.g.*, glucose, xylose, and sorbose, do not show thermal mutarotation. It is suggested that other monosaccharides derived from the *arabo*-configuration may also be found to mutarotate thermally, *e.g.*, fucose and altrose.

As a result of the above observations, the values for $[\alpha]_D$ of pure samples of methylated D-fructoses previously published (Bell and Palmer, *J.*, 1949, 2522; *J.*, 1952, 3763) must be considered unreliable since the air temperature of the polarimeter-room had been incorrectly assumed to represent that of the solution in the instrument. Differences of up to 3° have since been found to occur between these two temperatures. The temperature quoted by Albon, Bell, Blanchard, Gross, and Rundell (*J.*, 1953, 24) for the $[\alpha]_D$ of 1 : 3 : 4-trimethyl D-fructose from methylated kestose is, on the other hand, correct.

EXPERIMENTAL

All rotations were observed in water.

Sources of Material.—**1 : 3 : 4 : 6-Tetramethyl** D-fructose was obtained by chromatography (Bell and Palmer, *J.*, 1949, 2522) from the hydrolysate of methylated irisin and was free from detectable amounts of aldose derivatives or of hexamethyl difructose dianhydrides (cf. Bell and Palmer, *J.*, 1952, 3763). Thrice distilled at 70°/0·01 mm. the liquid had $[\alpha]_D^{20\cdot0}$ +30·3° and n_D^{20} 1·4506.

1 : 3 : 4 : 5-Tetramethyl D-fructose was prepared by methylation of β-methyl-D-fructopyranoside followed by hydrolysis of the glycoside. Thrice recrystallised from ether the sugar (prisms) had m. p. 99° and $[\alpha]_D^{20\cdot0}$ at equilibrium, −122°.

3 : 4 : 6-Trimethyl D-fructose, isolated chromatographically from hydrolysed trimethyl inulin as a colourless syrup, was thrice distilled in a high vacuum. No trace was found of anhydro-compounds. $[\alpha]_D^{20\cdot0}$ was +29·5° and n_D^{20} 1·4651.

1 : 3 : 4-Trimethyl D-fructose was isolated chromatographically from the hydrolysate of methylated grass levan. Thrice crystallised from carbon tetrachloride it had m. p. 73—75°, $[\alpha]_D^{20\cdot0}$ −55·7°.

3-Methyl D-fructose was kindly provided by Dr. W. B. Glen of Messrs. Ayerst, McKenna and Harrison, Montreal, Canada, and had been prepared through methylation of 1 : 2-4 : 5-di*iso*propylidene D-fructose (Glen, Grant, and Myers, *J.*, 1951, 2568). Thrice recrystallised from ethanol, the substance (needles) had m. p. 129°, $[\alpha]_D^{20}$ −100° (2 minutes), falling to −62·2° (const. after 21 hours).

1-Methyl D-fructose was also provided by Dr. Glen, in the form of a brown syrup obtained by hydrolysis of 1-methyl 2 : 3-4 : 5-di*iso*propylidene D-fructose (*idem*, *loc. cit.*). Evaporation of a solution treated with well-washed charcoal and a mixture of " Deacidite " and " Zeocarb " resins (cf. Wadman, *J.*, 1952, 3051) gave a colourless, stiff syrup having $[\alpha]_D^{20}$ −63·3° and n_D^{20} 1·5066 (decrease for *rise* in 1°, 0·00032).

Measurement of Rotations.—Roughly weighed amounts of the appropriate sugars were

placed in tared 25-ml. graduated flasks and dried to constant weight in a high vacuum over phosphoric anhydride and potassium hydroxide. [1 : 3 : 4 : 6-Tetramethyl D-fructose is volatile under these conditions (Bell and Palmer, *J.*, 1949, 2522); drying was therefore continued until a loss of ~10% of the original weight was obtained. n_D^{20} was then 1·4507.] Glass-distilled water was used to dissolve the sugars at room temperature and the solutions kept (~24 hours) until temperature-constant $[\alpha]_D$'s were attained. Observations were then made in a 4-dm. jacketed tube, at a minimum of six temperatures between 5·0° and 30·0°. To ensure that equilibria had been attained, polarimetric readings were taken over periods of 20 minutes, the solution being kept at the required temperature. No variations in $[\alpha]_D$'s were noted if the temperature was changed from a lower to a higher, or from a higher to a lower one, even if this was done over the extremes of the range examined. Equilibria were rapidly attained. Solutions of each sugar at three concentrations between 2 and 8% were examined; no "concentration effect" could be detected. In every instance straight-line plots were obtained between $[\alpha]_D$ and temperature.

The author is grateful to Dr. W. B. Glen for generous gifts of monomethyl fructoses and to Drs. G. D. Greville and D. H. Northcote for useful discussions.

THE BIOCHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 22nd*, 1952.]

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247. *Correlation of Vapour Pressure, Temperature, and Molar Entropy of Vaporisation.*

By LEO H. THOMAS.

It is shown that the ratio of the values of the differential $\boldsymbol{R}T\,\mathrm{d}\log_e p/\mathrm{d}T$ (where T is the absolute temperature) for any two non-associated liquids at the same vapour pressure p is a constant, and a generalised vapour pressure–temperature relation is presented. A reliable and accurate method is then given for comparison of vapour pressures, and procedures are developed for interpolation and extrapolation of vapour-pressure data.

IN continuation of work on comparison of latent heats of vaporisation at corresponding states (Thomas, *J.*, 1949, 3415), it has been found that the ratio of the values of the function $E/T = \boldsymbol{R}T\,\mathrm{d}\log_e p/\mathrm{d}T$ for any two non-associated liquids at temperatures corresponding to the same saturated vapour pressure p is a constant. At temperatures somewhat below the normal b. p., when the vapour behaves approximately as a perfect gas, E/T becomes, of course, L/T, the molar entropy of vaporisation.

Values of E/T have been calculated by numerical differentiation of recorded vapour-pressure data over as wide a range as possible, and then plotted as log E/T against log p. A series of sixteen selected vapour pressures log p_1, log p_2, . . . log p_n then being taken, the corresponding values of $\log(E/T)_1$, etc., were read off for a number of substances. Ideally, then, $\log(E/T)_n - \log(E/T)_{n-1}$ should be constant. These increments were averaged over the whole of the range to represent the behaviour of an ideal reference substance, and the latter assigned a convenient value E/T at 0·1 atm. of 100 cal. per mole per degree, *i.e.*, a Trouton constant of 100 at this pressure. Values of E/T at other vapour pressures then read as in Table 1.

TABLE 1.

V. p., atm.	E/T	V. p., atm.	E/T	V. p., atm.	E/T	V. p., atm.	E/T
0·001	141·1	0·020	115·4	1	77·8	20	52·6
0·002	135·7	0·050	106·8	2	71·3	30	50·0
0·005	127·9	0·25	91·3	5	62·6	40	48·1
0·010	121·8	0·50	84·6	10	57·1	50	47·2

The behaviour of a number of substances is compared with that of the ideal reference substance in Table 2. The figures represent $(E/T)_{\text{ideal}}$ divided by the corresponding values for the substances tabulated, and are constant within the limits of accuracy obtainable by the method.

The above definition of E leads to the expression $(T/E)\,\mathrm{d}\log_{10}p = \mathrm{d}T/2{\cdot}303\boldsymbol{R}T$, and integration gives

$$\log_{10} T_2/T_1 = \boldsymbol{R}\int_{\log_{10}p_1}^{\log_{10}p_2} (T/E)\,\mathrm{d}\log_{10}p$$

or, in terms of our ideal reference substance (suffix s):

$$\log_{10} T_2/T_1 = \boldsymbol{R}K\int_{\log_{10}p_1}^{\log_{10}p_2} (T/E)_s\,\mathrm{d}\log_{10}p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\log_{10} T = \log_{10}\theta + \boldsymbol{R}K\int_{0}^{\log_{10}p} (T/E)_s\,\mathrm{d}\log_{10}p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where θ is the absolute temperature corresponding to a vapour pressure of unity (1 mm. Hg), and K is a constant for a given substance as recorded in Table 2.

$(T/E)_s$ cannot apparently be expressed by a simple mathematical expression (compare Thodos, *Ind. Eng. Chem.*, 1950, **42**, 1514); instead, values of the standard integral have been evaluated graphically.

TABLE 2.

Substance	Refs.*	Vapour pressure, in atmospheres: p_e	0·001	0·002	0·005	0·010	0·020	0·050	0·10	0·25
(I) Et_2O	1, 2, 3	36	3·56	3·57	3·57	3·57	3·57	3·58	3·57	3·57
(II) CCl_4	1	45	—	—	—	—	3·67	3·67	3·66	3·67
(III) $CH_3{\cdot}CO_2Et$	1	38	—	—	—	—	—	3·44	3·41	3·41
(IV) C_6H_5Cl	1, 2	45	3·61	3·60	3·59	3·59	3·57	3·57	3·57	3·57
(V) C_2H_6	4	49	—	—	—	—	—	3·91	3·96	3·95
(VI) HCl	4	82	—	—	—	—	—	—	—	—
(VII) n-C_5H_{12}	1	33	—	—	—	—	3·71	3·70	3·71	3·73
(VIII) CO	5	35	—	—	—	—	—	—	—	4·22
(IX) n-C_6H_{14}	1, 2, 6	30	3·57	3·59	3·59	3·59	3·59	3·62	3·63	3·66
(X) C_6H_6	1	48	—	—	—	—	—	—	3·61	3·59
(XI) CCl_2F_2	7	40	—	—	—	—	—	—	—	3·81
(XII) $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ ...	1	34	—	—	—	—	—	3·41	3·39	3·39

Substance	Vapour pressure, in atmospheres: 0·50	1	2	5	10	20	30	40	Mean deviation, %
(I) Et_2O	3·59	3·59	3·61	3·59	3·59	3·58	3·57	—	0·3
(II) CCl_4	3·66	3·67	3·69	3·71	3·71	3·69	3·67	3·64	0·5
(III) $CH_3{\cdot}CO_2Et$	3·41	3·39	3·39	3·38	3·37	3·35	3·35	—	0·6
(IV) C_6H_5Cl	3·57	3·58	3·59	3·57	3·51	—	—	—	0·4
(V) C_2H_6	3·93	3·92	3·91	3·91	3·89	3·90	3·91	—	0·4
(VI) HCl	—	3·65	3·63	3·59	3·59	3·59	3·63	—	0·6
(VII) n-C_5H_{12}	3·73	3·72	3·73	3·70	3·69	3·67	3·67	—	0·5
(VIII) CO	4·21	4·18	4·19	4·20	4·22	4·23	4·22	—	0·3
(IX) n-C_6H_{14}	3·67	3·65	3·66	3·62	3·63	3·59	—	—	0·7
(X) C_6H_6	3·57	3·58	3·59	3·61	3·61	3·61	3·59	3·58	0·3
(XI) CCl_2F_2	3·79	3·79	3·79	3·77	3·77	3·80	3·82	—	0·3
(XII) $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ ...	3·39	3·41	3·41	3·43	3·42	—	—	—	0·3

* (1) Young, *Sci. Proc. Roy. Soc. Dublin*, 1909–10, **12**, 374. (2) Mündel, *Z. phys. Chem.*, 1913, **85**, 435. (3) Taylor and Smith, *J. Amer. Chem. Soc.*, 1922, **44**, 2450. (4) International Critical Tables. (5) Crommelin, Byleveld, and Brown, *Proc. K. Akad. Wetensch.*, 1931, **34**, 1314. (6) Drücker, Jimeno, and Kangro, *Z. phys. Chem.*, 1915, **90**, 513. (7) Gilkey, Gerard, and Bixler, *Ind. Eng. Chem.*, 1931, **23**, 364.

TABLE 3. *Evaluation of the standard integral.*

$\log_{10} p_{(\mathrm{mm.})}$; range, 0 to	−0·4	−0·2	+0·2	+0·4	+0·6	+0·8	1·0
Corr. value for integral from zero	0·002804	0·001420	0·001458	0·002956	0·004500	0·006092	0·007738
$\log_{10} p_{(\mathrm{mm.})}$; range, 0 to	1·2	1·4	1·6	1·8	2·0	2·2	2·4
Corr. value for integral from zero	0·009442	0·011216	0·013062	0·014986	0·016992	0·019088	0·021288
$\log_{10} p_{(\mathrm{mm.})}$; range, 0 to	2·6	2·8	3·0	3·2	3·4	3·6	3·8
Corr. value for integral from zero	0·023608	0·26058	0·028650	0·031394	0·034306	0·037402	0·040712
$\log_{10} p_{(\mathrm{mm.})}$; range, 0 to	4·0	4·2	4·4	4·6			
Corr. value for integral from zero	0·044228	0·047954	0·051896	0·056060			

Solution of (2) by application of Campbell's " zero-sum " method (*Phil. Mag.*, **1920**, **39**, 177; **1924**, **47**, 816) then gave for ether

$$\log_{10}(T/100) = 0{\cdot}29506 + 7{\cdot}1280\int_{0}^{\log_{10}p}(T/E)_p\,\mathrm{d}\log_{10}p$$

(0° K = −273·15° C). The measure of agreement between T at the published vapour pressures and those calculated from the equation is shown in Table 4 (t = °C). In view of the fact that the measurements over the three ranges 0·444—0·949, 3·95—437·7 mm., and 921 mm. to the critical point are those of three independent experimenters (see refs. in Table 2), the agreement is remarkable, and must surely be within the limits of absolute experimental accuracy. An examination of the mean % deviations printed in Table 2 suggests that a comparable degree of accuracy is to be generally expected from critical conditions to at least as low a vapour pressure as, say, 0·5 mm. of mercury.

TABLE 4.

V. p., mm.	t, calc.	t, exptl.	Error	V. p., mm.	t, calc.	t, exptl.	Error
0·443	−83·8°	−83·5°	−0·3°	921	40·11°	40·00°	+0·11°
0·949	−76·4	−76·2	−0·2	1,734	60·12	60·00	+0·12
3·95	−60·85	−60·80	−0·05	4,855	99·80	100·00	−0·20
12·62	−46·01	−46·00	−0·01	7,513	120·03	120·00	+0·03
34·03	−31·25	−31·33	+0·08	15,778	139·98	160·00	−0·02
104·8	−11·52	−11·64	+0·12	21,775	179·85	180·00	−0·15
437·7	19·84	19·87	−0·03	27,060 *	194·2	193·8 *	+0·4

* Critical values.

From (2) we get for two substances at the same vapour pressure :

$$\log_{10} T_1/\theta_1 = (K_1/K_2)\log_{10} T_2/\theta_2$$

or,

$$\log_{10} T = I + (K_1/K_2)\log_{10} T_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where I is a constant—a modification of the well-known Ramsay–Young relationship.

Equation (3) is far easier to use than that previously proposed by the author (*loc. cit.*), and it does not suffer from the limitation that it can be used only in regions where the ideal-gas laws can be considered as valid. A knowledge or reliable estimation of critical data is also not now required. The previously proposed equation is still, however, useful as a method of extrapolating to low vapour pressures (*loc. cit.*, p. 3419).

Table 5 records the behaviour of a number of substances compared with that of benzene. Most probable vapour-pressure values for the latter have been determined graphically (direct p–T plot) from Timmermans's data (" Physico-chemical Constants of Pure Organic Compounds," Elsevier Pub. Co. Ltd., 1950, 142), supplemented above 100° by those of von Huhn (*Forsch. Gebiete Ingenieurw.*, 1931, *A*, **2**, 109), Gornowski, Amick, and Hixson (*Ind. Eng. Chem.*, **1947**, **39**, 1348), and Bender, Furukawa, and Hyndman (*ibid.*, 1952, **44**, 387).

The most recent and probably the most accurate measurements are those of Forziati, Norris, and Rossini (*J. Res. Nat. Bur. Stand.*, 1949, **43**, 555) in the range 48—780 mm. They differ from the author's most probable values by $\gtrless 0{\cdot}2°$ at any of the twenty literature values (mean difference = 0·1°) and are related to the latter by the equation

$$\log_{10}(T/100) = 1{\cdot}0030\log_{10}(T/100)_{\text{selected}} - 0{\cdot}0015 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The constants of Table 5, evaluated in the manner already described, were calculated by expressing each temperature to the nearest 0·1°—a procedure which, apart from experimental error, would result in a mean difference between actual and calculated temperatures of 0·01—0·05% depending on the b. p. of the substance. The vapour pressures used in this table ranged in general from about 36 mm. (v. p. of benzene at its f. p.) to ~760 mm. Four-figure logarithms were used in the calculations so the average agreement between actual and calculated temperatures cannot, except by chance, be better than corresponds to an error of 0·02—0·03%.

The average error in using measurements carried out by the National Bureau of

Standards and by similar methods (refs. 5—9) is 0·02%. The errors for other measurements, however, average 0·04%, corresponding to an error of ~0·1° for a substance of b. p. −100° and to 0·2° for one of b. p. 300°. In no case have the errors in the individual determinations been such as to imply departure from linearity in the log T–log T_{benzene} plot.

A more stringent test is possible for measurements by the National Bureau of Standards since b. p.s are taken at a series of set and almost constant pressures. It is then possible

TABLE 5.

$\log_{10}(T/100) = A + B \log_{10}(T/100)_{\text{benzene}}$

Substance	B	A	Mean error, %	B. p., °K	Ref.*
H_2	1·800	−1·6761	0·03°	20	1
O_2	1·159	−0·6804	0·03	90	2
CH_4	1·182	−0·6005	0·05	111	3
C_2H_6	1·097	−0·3355	0·01	184	3
C_3H_8	1·065	−0·2199	0·04	231	3
Cl_2	1·030	−0·1873	0·03	238	4
C_4H_{10}	1·052	0·1410	0·01	273	3
cis-CHMe:CHMe	1·032	0·1235	0·01	277	5
C_5H_{12}	1·029	0·0741	0·05	309	3
CS_2	1·054	0·0739	0·03	319	4
$COMe_2$	0·9761	0·0173	0·03	329	4
$CHCl_3$	0·9954	0·0221	0·04	334	4
C_6H_{14}	1·015	0·0222	0·03	342	3
C_7H_{16}	0·9943	0·0251	0·04	353	3
$CH_2Pr^nPr^i$	1·008	0·0075	0·03	363	6
$[CH_2]_4$>CHEt	1·015	0·0193	0·02	376	6
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}NO_2$	0·9703	0·0753	0·03	404	7
Bu^nCN	0·9754	0·0827	0·02	414	8
n-$(C_5H_{11})_2O$	0·9404	0·1472	0·03	460	8
$C_{20}H_{42}$	0·9322	0·1788	0·02	489	9
$COPh_2$	0·9154	0·2610	0·02	579	8
SnI_4	1·032	0·2284	0·06	621	10
Hg	1·006	0·2489	0·02	630	11
Zn	0·9548	0·5537	0·02	1180	12
KOH	1·092	0·6060	0·08	1600	12
Bi	0·5690	0·9177	0·09	1693	12

* (1) Henning, *Z. Physik*, 1926, **40**, 775. (2) Jaquerod, Travers, and Senter, *Proc. Roy. Soc.*, 1902, **70**, 484. (3) From Thodos's compilation, *loc. cit.* (4) International Critical Tables. (5) Scott, Ferguson, and Brickwedde, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 1. (6) Forziati, Norris, and Rossini, *loc. cit.* (7) Holcomb and Dorsey, *Ind. Eng. Chem.*, 1949, **41**, 2788. (8) Dreisbach and Shrader, *ibid.*, p. 2879. (9) Willingham, Taylor, Pignocco, and Rossini, *J. Res. Nat. Bur. Stand.*, 1945, **35**, 219. (10) Kabesh and Nyholm, *J.*, 1951, 3245. (11) Ramsay and Young, *J.*, 1886, **49**, 37. (12) From "Chemical Engineers' Handbook" (Perry, 2nd edn., McGraw-Hill Co., 1941).

TABLE 6.

T_{nonane}, exptl. (to nearest 0·01°)	T_{benzene}, exptl.	Error	$\Delta \log_{10} T$, benzene	$\Delta \log_{10} T$, nonane	B
424·84°	354·02°	±0·00°			
			0·00854	0·00827	0·969
416·83	347·13	±0·00			
			0·01690	0·01635	0·968
401·43	333·88	±0·00			
			0·01551	0·01505	0·970
387·78	322·17	−0·01			
			0·01368	0·01320	0·965
376·15	312·18	±0·00			
			0·01138	0·01101	0·967
366·73	304·10	+0·01			
			0·01119	0·01082	0·967
357·71	296·37	+0·01			
			0·01297	0·01258	0·970
347·50	287·65	−0·01			

to apply (3) without involving interpolation uncertainties. Thus to the nearest 0·01°, the behaviour of nonane may be expressed in terms of that of benzene (both sets of vapour pressure being due to Willingham *et al.*, *loc. cit.*) by the equation

$$\log_{10}(T/100)_{\text{nonane}} = 0{\cdot}09687 + 0{\cdot}96781 \log_{10}(T/100)_{\text{benzene}}$$

The error in no single temperature exceeds 0·01°, so the actual mean error is less than this—in fact, the authors claim a reproducibility at a given vapour pressure of ±0·002°. It should also be observed that the value of the constant $B = K_1/K_2$ can be accurately ascertained by the slope between any two successive temperatures differing by not more than a few degrees (Table 6).

Remaining critical data are those tabulated by Timmermans (*op. cit.*).

Interpolation of Vapour Pressures.—It is obvious from the constancy of B in Table 6 that interpolation errors in the case of nonane, and indeed for substances in general, will be no greater than the experimental error.

Extrapolation of Vapour Pressures.—Method 1. Use of the constants of Table 5 and the critical temperatures recorded in the literature leads to calculated critical pressures for some paraffins as shown in Col. 4 of Table 7. They are seen to be too low by a mean of

TABLE 7.

Substance	T_c, °K	Corr. temp., benzene	p_c, calc., atm.	Lit. values	Error, % (method 1)	Error, % (modified)	Error, % (method 2)	V. p. used *
Ethane ...	305·3	286·2°	46·7	48·6, 48·8, 48·2	−3·7	−2·3	−3·0	1138·0 57·68
Propane ...	369·9	276·5	41·6	42·0	−1·0	±0·0	−1·7	760·0 37·39
Butane ...	426·3	266·9	36·8	35·7	−0·3	+1·1	+1·4	760·0
,, ...	425·2 †	265·6	36·2	37·5 †				36·26
Pentane ...	470·3	257·9	32·7	33·1	−1·2	±0·0	+0·6	760·0 44·64
Hexane ...	507·9	248·6	28·8	29·9, 29·6, 30·1	−3·3	−2·3	−1·6	760·0 41·35
Heptane ...	540·0	241·4	26·1	27·0, 26·9	−3·0	−2·2	−0·6	760·0 36·15

* Refs. as in Table 5.
† Beattie, Simard, and Su, *J. Amer. Chem. Soc.*, 1939, **61**, 924.

2·2%. Modified values calculated by use of equation (4) and the accurate measurements of the National Bureau of Standards lie nearer to the experimental. A further slight adjustment of the vapour pressure of benzene, either below the b. p. or in the region above, say, 25 atm., could completely account for the discrepancy.

Method 2. Col. 8 shows values calculated from equation (2) by using only two vapour pressures, ~760 and ~40 mm. The average error is now 1·6% but the distribution is more normal.

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248. p-*Aminodimethylaniline. Part VI.* Some Cationoid Halogenations* meta *to a Dimethylamino-group.*

By JOHN H. GORVIN.

Halogenation of dimethylaniline derivatives in concentrated sulphuric acid in presence of silver sulphate has given products in which the chlorine or bromine atom lies *meta* to the basic group. The applicability of the reaction depends on the nature of the other substituents present. The process has been applied in particular to the preparation of 4-amino-3-bromodimethylaniline.

THE method of cationoid halogenation of aromatic compounds in sulphuric acid in presence of silver sulphate (Derbyshire and Waters, *J.*, 1950, 573, 3694; Barker and Waters, *J.*, 1952, 150; Gorvin, *Chem. and Ind.*, 1951, 910; cf. Birckenbach and Goubeau, *Ber.*, 1933, **66**, 1283) has now been utilised for the direct introduction of a halogen atom *meta* to a dialkylamino-group. Thus bis-*p*-dimethylaminophenylmethane, which gives the 2 : 2′-dinitro-compound when nitrated in concentrated sulphuric acid, correspondingly gave the 2 : 2′-dibromo-compound in 80—85% yield when shaken in concentrated sulphuric acid with bromine and silver sulphate. The analogous chlorination gave the 2 : 2′-dichloro-derivative in 77% yield. The compounds were identified by comparison with authentic specimens (cf. Jones and Mason, *J.*, 1934, 1190).

* Part V, *J.*, 1951, 1697.

In the preparation of 4-amino-3-bromodimethylaniline this procedure could be either applied directly to a *p*-acylaminodimethylaniline or used to obtain the intermediate *m*-bromodimethylaniline from dimethylaniline. Bromination of both *p*-acetamido- and *p*-formamido-dimethylaniline proceeded very slowly in sulphuric acid, so that the theoretical yield of silver bromide was not obtained after 48 hours; the only products isolated were 4-acetamido-3-bromo- (70%) and 3-bromo-4-formamido-dimethylaniline (54%) respectively. The position of entry of the Br^+ cation therefore corresponds to that of the NO_2^+ cation (Hodgson and Crook, *J.*, 1932, 2976). The sluggishness of the reaction is consistent with partial inhibition of nuclear substitution *ortho* to an acylamino-group owing to steric hindrance (cf. Ungnade and Hansbury, *J. Org. Chem.*, 1952, **17**, 742), but the effect is possibly complicated by salt formation (MacMillan, *J.*, 1952, 4020). The introduction of a deactivating group into *p*-acetamidodimethylaniline inhibited the reaction completely; 4-acetamido-*NN*-dimethyl-2-nitroaniline (Part II, *J.*, 1942, 755) was recovered unchanged in 78% yield after 6 days' exposure to the brominating medium.

Cationoid bromination of dimethylaniline resembled the corresponding nitration (Groll, *Ber.*, 1886, **19**, 198; cf. Fitch, *Org. Synth.*, 1947, **27**, 62) in that a quantity (*ca.* 20%) of the *p*-isomer was formed, but in this case there was isolated in addition some 3 : 4-dibromodimethylaniline (*ca.* 7%). The main product, *m*-bromodimethylaniline (*ca.* 64%), was difficult to obtain free from the *p*-isomer and unchanged dimethylaniline, but for the immediate purpose this step was unnecessary; when the mixed bases were nitrosated in dilute hydrochloric acid 3-bromo-*NN*-dimethyl-4-nitrosoaniline hydrochloride separated together with a little *NN*-dimethyl-*p*-nitroaniline. The nitroso-compound (*ca.* 33% based on dimethylaniline) could be satisfactorily reduced to 4-amino-3-bromodimethylaniline (Kharasch and Piccard, *J. Amer. Chem. Soc.*, 1920, **42**, 1855). The 3 : 4-dibromodimethylaniline formed in the reaction may have been derived from either or both of the isomers (cf. Vorländer, *Ber.*, 1919, **52**, 282); *p*-bromodimethylaniline is slowly brominated in concentrated sulphuric acid, to yield the 3 : 4-dibromo-compound as sole product.

Cationoid chlorination of dimethylaniline was essentially analogous to the bromination. From the resulting mixture of bases was obtained 3-chloro-*NN*-dimethyl-4-nitrosoaniline hydrochloride (*ca.* 28% based on dimethylaniline), readily reduced to 4-amino-3-chloro-dimethylaniline (cf. Part III, *J.*, 1946, 532). From a specimen of the mixed bases, freed from *m*-chlorodimethylaniline and unchanged dimethylaniline by diazotised sulphanilic acid, was obtained *p*-chlorodimethylaniline (*ca.* 20%). No 3 : 4-dichloro-compound could be isolated in this reaction, but it was subsequently established that *p*-chlorodimethylaniline is chlorinated normally, but very slowly, in concentrated sulphuric acid to give the previously unknown 3 : 4-dichlorodimethylaniline, identical with the product obtained from diazotised 4-amino-3-chlorodimethylaniline by the Sandmeyer procedure. The impression that chlorine reacts less readily than bromine under the conditions used is supported by the failure to achieve the cationoid chlorination of *p*-acetamidodimethylaniline; after 48 hours only unchanged material (65%) could be isolated.

The use of carbon tetrachloride as a solvent for chlorine in this type of chlorination (Gorvin, *loc. cit.*) is satisfactory only with substances which react rapidly under the conditions employed. In presence of silver sulphate the independent reaction between carbon tetrachloride and sulphuric acid (cf. Grignard and Urbain, *Compt. rend.*, 1919, **169**, 17; Mauguin and Simon, *ibid.*, p. 34) proceeds slowly at room temperature with withdrawal of Ag^+ cations from the system as silver chloride; consequently the yield of chlorination product is reduced. The amount of silver chloride produced when carbon tetrachloride reacts with an excess of sulphuric acid is in agreement with the essentially hydrolytic scheme:

$$CCl_4 + HO{\cdot}SO_3H = COCl_2 + 2HCl + SO_3$$

since the chlorosulphonic acid usually written in the equation is unstable under these conditions (Williams, *J.*, 1869, **22**, 306). Although *p*-nitrotoluene is chlorinated so rapidly that there is little interference from the competing reaction, bis-*p*-dimethylaminophenylmethane reacted more slowly and the presence of carbon tetrachloride reduced the yield

of 2 : 2′-dichloro-derivative from 77% to 39%. The fairly rapid chlorination of benzoic acid gave products of a nature substantially unaffected by the presence of the solvent, but with dimethylaniline the final yield of 4-amino-3-chlorodimethylaniline, isolated as the acetyl derivative, was reduced to half. An attempt to chlorinate *p*-chlorodimethylaniline under similar conditions resulted only in the recovery of unchanged material. The use of a solvent for chlorine is not however really necessary, since large amounts of material can be chlorinated in a reasonably sized flask by shaking in an atmosphere of chlorine; the progress of the reaction may be followed by the fall in pressure and further amounts of chlorine introduced as required.

From a theoretical standpoint these halogenation results provide further evidence for the concept, based mainly on nitration studies, of the substantial inhibition of the *ortho-para*-directing power of the dialkylamino-group by salt formation in concentrated sulphuric acid and its replacement by the *meta*-directing influence of the $-NHR_2^+$ group. The procedure, which is likely to find application chiefly among dialkylanilines already containing an *ortho-para*-directing group in the *para*-position, is distinguished by the exceptional ease of recovery of silver halide, and of subsequent isolation of the product; losses due to concurrent sulphonation or other side reactions were not considerable in the examples studied.

Experimental

Di-(2-bromo-4-dimethylaminophenyl)methane.—A solution of bis-*p*-dimethylaminophenylmethane (2·54 g., 0·01 mol.) and silver sulphate (3·12 g., 0·01 mol.) in concentrated sulphuric acid (30 c.c.) was shaken with bromine (3·2 g., 0·02 mol.). Heat was evolved and after 2 hours the theoretical amount of silver bromide was obtained on filtration. The filtrate was poured into ice-water containing sodium sulphite and neutralised with ammonia. The crude product (3·98 g., 97%; m. p. 95—97°) formed needles (80—85%) (from ethanol), m. p. 103—104°, not depressed by di-(2-bromo-4-dimethylaminophenyl)methane prepared by the Sandmeyer procedure from di-(2-amino-4-dimethylaminophenyl)methane. The pure product had m. p. 104—105° (Found: C, 49·5; H, 4·9; Br, 38·2. Calc. for $C_{17}H_{20}N_2Br_2$: C, 49·5; H, 4·9; Br, 38·8%) (Jones and Mason, *loc. cit.*, reported m. p. 103°).

Di-(2-chloro-4-dimethylaminophenyl)methane.—A solution of bis-*p*-dimethylaminophenylmethane (1·27 g., 0·005 mol.) and silver sulphate (1·56 g., 0·005 mol.) in concentrated sulphuric acid (20 c.c.) was shaken with excess of dry chlorine in a stoppered 500-c.c. flask fitted with a tap. After 4 hours pressure ceased to fall. The excess of chlorine was removed in a current of air and the acid solution poured into ice-water containing sodium sulphite. After removal of silver chloride (quantitative) the filtrate was neutralised and extracted with ether, to give crude di-(2-chloro-4-dimethylaminophenyl)methane (1·6 g.) as an oil which rapidly solidified (m. p. 89—92°). One crystallisation from ethanol gave 1·25 g. (77%), m. p. 97°, and further crystallisation gave needles, m. p. 99—100°, unchanged by authentic material, m. p. 99—100°, prepared from di-(2-amino-4-dimethylaminophenyl)methane (Jones and Mason, *loc. cit.*, gave m. p. 96°; von Braun and Kruber, *Ber.*, 1913, **46**, 3463, reported m. p. 96—97°) (Found: C, 63·3; H, 6·2; Cl, 21·65. Calc. for $C_{17}H_{20}N_2Cl_2$: C, 63·2; H, 6·2; Cl, 21·9%).

Passage of a slow stream of dry chlorine for 6½ hours through a sulphuric acid solution of the reactants gave only an 85% recovery of silver chloride and a 48% yield of 2 : 2′-dichloro-derivative purified to m. p. 95—96°.

4-*Acetamido-3-bromodimethylaniline.*—A solution of *p*-acetamidodimethylaniline (1·78 g., 0·01 mol.) and silver sulphate (1·56 g., 0·005 mol.) in concentrated sulphuric acid (25 c.c.) was shaken with bromine (1·6 g., 0·01 mol.) for 48 hours and then poured into ice-water containing sodium sulphite. The silver bromide (1·5 g., 80%) was removed and the filtrate neutralised with ammonia, whereupon 4-*acetamido-3-bromodimethylaniline* (1·66 g., 65%; m. p. 121—123°) separated. A further 5% was obtained by ether-extraction of the filtrate. The acetyl derivative formed square platelets (from aqueous ethanol), m. p. 123·5—124·5°, unchanged by admixture with the acetylation product of 4-amino-3-bromodimethylaniline prepared from *m*-bromodimethylaniline (Kharasch and Piccard, *loc. cit.*) (Found: C, 47·1; H, 5·2; Br, 31·4. $C_{10}H_{13}ON_2Br$ requires C, 46·7; H, 5·1; Br, 31·1%).

Shaking for 24 hours only gave a 70% recovery of silver bromide and a 55% total yield of acetyl derivative, m. p. 121—123°.

3-*Bromo-4-formamidodimethylaniline.*—*p*-Formamidodimethylaniline (1·64 g., 0·01 mol.) was brominated in a similar manner; again the reaction was sluggish and after 48 hours the

yield of silver bromide was 1·6 g. (85%). Neutralisation gave a precipitate of 3-*bromo*-4-*formamidodimethylaniline* (1·3 g., 54%; m. p. 116—118°), which separated from aqueous ethanol in felted needles, m. p. 118·5—119·5° (Found: C, 44·6; H, 4·6. $C_9H_{11}ON_2Br$ requires C, 44·5; H, 4·6%). Its structure was verified by hydrolysis (50% sulphuric acid) and acetylation of the resulting base to 4-acetamido-3-bromodimethylaniline.

Bromination of Dimethylaniline in Sulphuric Acid.—(a) *General procedure.* A solution of dimethylaniline (4·84 g.) and silver sulphate (6·42 g.) in concentrated sulphuric acid (50 c.c.) was shaken overnight with bromine (6·4 g.); heat of reaction was apparent after 5 minutes. Silver bromide was precipitated quantitatively. The acid solution, adjusted to pH 2—3, gave 3 : 4-dibromodimethylaniline (*ca.* 0·76 g., 7%) on being kept at 0°; this crystallised from dilute hydrochloric acid and from light petroleum (b. p. 40—60°) in needles or hexagonal plates, m. p. 66·5—67°, not depressed by 3 : 4-dibromodimethylaniline prepared by the bromination of *m*-bromodimethylaniline (Found: Br, 57·4. Calc. for $C_8H_9NBr_2$: Br, 57·3%). The picrate (yellow leaflets) had m. p. 150—151° (Found: Br, 31·3. Calc. for $C_{14}H_{12}O_7N_4Br_2$: Br, 31·5%). Vorländer and Siebert (*Ber.*, 1919, **52**, 290) record m. p. 69—70° for the base and m. p. 142—146° for the picrate.

The filtrate from 3 : 4-dibromodimethylaniline was brought to a standard volume: 30% of the solution was shaken for 2 hours at pH 3—4 with a diazo-solution prepared from sulphanilic acid (2·5 g.). The resulting mixture was made alkaline and extracted with ether to give an oil (0·5 g.) which solidified. This, when freed from traces of 3 : 4-dibromodimethylaniline by adjustment of the pH of an acidic solution, gave *p*-bromodimethylaniline (*ca.* 20%), characterised by its mixed m. p. with authentic material and through the picrate, m. p. 136—138° (Fahim and Galaby, *J.*, 1950, 3531, record m. p. 136—137°).

A further volume (5%) of the standard solution was coupled with a diazo-solution prepared from *p*-nitroaniline. The yield of crude azo-compound was *ca.* 71%. After allowance for the presence of 7% of unchanged dimethylaniline (corresponding to the amount of 3 : 4-dibromo-compound), the maximum amount of *m*-bromodimethylaniline in the mixture was *ca.* 64%. Attempts to obtain *m*-bromodimethylaniline free from the *p*-isomer and dimethylaniline were only partly successful.

(b) *Nitrosation of bromination product.* In a bromination of the type described above there were obtained on neutralisation of the sulphuric acid solution and extraction with ether 7·2 g. (90%) of an oil. This was dissolved in a mixture of hydrochloric acid (20 c.c.; *d* 1·2) and water (65 c.c.), and sodium nitrite (5·1 g.) in water (24 c.c.) was run in at 0°, followed by 10% hydrochloric acid (13 c.c.). After 3 hours the precipitate was collected, washed with 3% hydrochloric acid (25 c.c.), and dried. The powdered material was washed with dry ether, and the suspension filtered, to give 3-bromo-*NN*-dimethyl-4-nitrosoaniline hydrochloride in *ca.* 33% yield (based on dimethylaniline): the ethereal filtrate on slow evaporation gave crystals of *NN*-dimethyl-*p*-nitroaniline (*ca.* 2%) derived from unchanged dimethylaniline present in the oil.

(c) *Reduction of the nitroso-compound.* The method of Kharasch and Piccard (*loc. cit.*) gave the base which was acetylated and reprecipitated from acetic acid with ammonia to give 4-acetamido-3-bromodimethylaniline, m. p. 122—123°, in *ca.* 22% yield (based on dimethylaniline).

A comparable bromination of dimethylaniline in 100% sulphuric acid gave results essentially similar to those obtained in the ordinary concentrated acid.

Bromination of p-*Bromodimethylaniline in Sulphuric Acid.*—A solution of the base (2·0 g.) and silver sulphate (1·56 g.) in concentrated sulphuric acid (20 c.c.) was shaken with bromine (1·6 g.). Reaction was sluggish, and the recovery of silver bromide after 24 hours was 74%. At pH 2—3 there was precipitated 3 : 4-dibromodimethylaniline (0·9 g., 46%), m. p. 67°, unchanged by previously obtained samples. The filtrate on adjustment of pH afforded a further amount of product in addition to unchanged *p*-bromodimethylaniline.

Chlorination of Dimethylaniline in Sulphuric Acid.—A solution of dimethylaniline (2·42 g.) and silver sulphate (3·12 g.) in concentrated sulphuric acid (25 c.c.) was shaken with excess of dry chlorine in a 1-l. flask fitted with a tap; the reaction appeared to be complete in *ca.* 2½ hours. It was left overnight and worked up in the usual way. The recovery of silver chloride was quantitative. On neutralisation and extraction with ether, *ca.* 95% of mixed bases was obtained. The oil, dissolved in a mixture of hydrochloric acid (10 c.c.; *d* 1·2) and water (35 c.c.), was treated at 0° with sodium nitrite (2·2 g.) in water (20 c.c.); subsequently 10% hydrochloric acid (20 c.c.) was added. After 5 hours at 0° the precipitated 3-chloro-*NN*-dimethyl-4-nitrosoaniline hydrochloride was filtered off, washed with 3% hydrochloric acid (15 c.c.), and dried. The powdered material after being washed with dry ether weighed 1·23 g.

(28% based on dimethylaniline). Stannous chloride reduction and subsequent acetylation converted it into 4-acetamido-3-chlorodimethylaniline (19%), m. p. 116—117°. Recrystallisation from aqueous alcohol gave needles, m. p. 117—118°, unchanged by authentic material (Part III).

The mixed bases obtained in a similar experiment (in which 100% sulphuric acid was used) were treated with diazotised sulphanilic acid as described for the corresponding bromination. The uncoupled base gave no precipitate at pH 2. It was purified through its picrate (crude yield, *ca.* 20%) and had m. p. 35°, unchanged by *p*-chlorodimethylaniline (Part I). p-*Chlorodimethylaniline picrate* crystallised from ethanol in needles, m. p. 126—128° (Found: C, 43·8; H, 3·5; Cl, 9·3. $C_{14}H_{13}O_7N_4Cl$ requires C, 43·7; H, 3·4; Cl, 9·2%).

3 : 4-*Dichlorodimethylaniline.*—(*a*) A solution of *p*-chlorodimethylaniline (1·07 g.) and silver sulphate (1·07 g.) in concentrated sulphuric acid (15 c.c.) in a 250-c.c. flask fitted with a tap, was shaken with excess of chlorine for 60 hours, then left for 120 hours. The solution was worked up in the usual way and 3 : 4-*dichlorodimethylaniline* (0·79 g., 61%; m. p. 37—39°) was precipitated at pH 2—3. It was very soluble in light petroleum (b. p. 40—60°), but crystallised from dilute hydrochloric acid in needles, m. p. 38—39° (Found: C, 50·4; H, 5·1; Cl, 37·3. $C_8H_9NCl_2$ requires C, 50·55; H, 4·8; Cl, 37·3%). Its *picrate* crystallised from ethanol in flakes, m. p. 138—139° (Found: Cl, 17·1. $C_{14}H_{12}O_7N_4Cl_2$ requires Cl, 16·9%). The aqueous filtrate from the dichloro-compound was brought to pH 10; unchanged *p*-chlorodimethylaniline (0·1 g., 9%, m. p. 35°) slowly crystallised.

(*b*) 4-Acetamido-3-chlorodimethylaniline (0·74 g.) was hydrolysed with hydrochloric acid, and the solution diazotised and added to excess of cuprous chloride in hydrochloric acid at 80°. After neutralisation with ammonia the mixture was steam-distilled. Ether-extraction of the distillate gave an oil (0·37 g.) which afforded a picrate (0·59 g.), m. p. 135—136°, not depressed by 3 : 4-dichlorodimethylaniline picrate described above. The base, regenerated from the picrate and crystallised from dilute hydrochloric acid, had m. p. 38—39°, unchanged by 3 : 4-dichlorodimethylaniline.

Reaction of Carbon Tetrachloride with Sulphuric Acid.—Carbon tetrachloride (1·54 g., 0·01 mol.) was shaken with a solution of silver sulphate (6·24 g., 0·02 mol.) in concentrated sulphuric acid (15 c.c.). Carbonyl chloride was evolved. The silver chloride was filtered off after 4 hours, washed with water and alcohol, and dried: its weight (2·86 g.) was equivalent to the formation of 2HCl from each molecule of CCl_4. No further precipitation of silver chloride occurred in the filtrate on storage; after passage of a current of dry air for an hour and subsequent dilution only a slight precipitate was formed as a result of the hydrolysis of residual carbonyl chloride.

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249. *Usnic Acid. Part VIII.* C-Diacetyl Derivatives of Phloroglucinol and C-Methylphloroglucinol.*

By F. M. DEAN and ALEXANDER ROBERTSON.

By means of boron trifluoride, diacetylphloroglucinol and 2 : 4-diacetyl-6-methylphloroglucinol together with their methyl ethers have been prepared by the *C*-acylation of phloroglucinol, *C*-methylphloroglucinol, and their mono- and di-methyl ethers. This procedure has also been shown to be convenient for the preparation of 2 : 4- and 4 : 6-diacetylresorcinol.

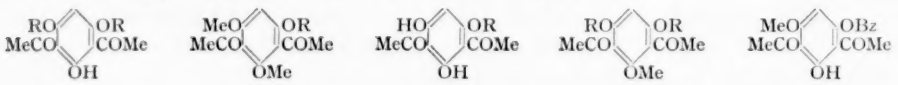
DURING exploratory studies on the synthesis and degradation of usnic acid and its isomeride usnolic acid it became necessary to examine the preparation and alkylation of diacetylphloroglucinol and its *C*-methyl derivative. Boron trifluoride, under the requisite conditions, has now been found to be a suitable reagent for *C*-acetylation of phloroglucinol derivatives and the method has been extended to the preparation of 2 : 4- and 2 : 6-diacetylresorcinol (cf., *e.g.*, Baker, *J.*, 1934, **71**, 1684; Desai and Mavani, *J. Indian Acad. Sci.*, 1949, **29**, *A*, 268; Phillips, Robertson, and Whalley, *J.*, 1952, 4951).

* Part VII, *J.*, 1939, 1594.

As originally prepared by the condensation of phloroglucinol and acetyl chloride with ferric chloride (Nencki, *Ber.*, 1899, **32**, 2417; Goschke and Tambor, *ibid.*, 1912, **45**, 1237) diacetylphloroglucinol is accompanied by triacetylphloroglucinol which, however, is formed in better yield by a Fries reaction on phloroglucinol triacetate (Klarmann, *J. Amer. Chem. Soc.*, 1926, **48**, 2358). Similarly, by the Friedel–Crafts reaction on *O*-dimethylphloroglucinol Tutin and Caton (*J.*, 1910, **97**, 2062) obtained a dimethyl ether of diacetylphloroglucinol which was shown by Gruber and Traub (*Monatsh.*, 1947, **77**, 414) to be the 1 : 5-dimethyl ether which they also prepared in 14% yield from phloracetophenone 2 : 4-dimethyl ether by the Hoesch reaction.

By the boron trifluoride method at room temperature an excellent yield of diacetylphloroglucinol (I; R = H) has been obtained whilst at higher temperatures the product contained some triacetylphloroglucinol which, under the requisite conditions, became the major component. Similarly, phloroglucinol monomethyl ether gave diacetylphloroglucinol 1-methyl ether (III; R = Me) which was not identical with the compound described by Gruber and Traub (*loc. cit.*). It may well be that the compound, m. p. 255—257°, formed by the Hoesch reaction and considered by these authors to be diacetylphloroglucinol 1-methyl ether was unchanged ketimine. *O*-Dimethylphloroglucinol and one molecular proportion of acetylating agent yielded phloracetophenone 2 : 4-dimethyl ether with only traces of phloracetophenone 2 : 6-dimethyl ether, unlike the product from the corresponding Hoesch reaction (Canter, Curd, and Robertson, *J.*, 1931, 1245). With the necessary quantity of acetylating reagent *O*-dimethylphloroglucinol and phloracetophenone 2 : 4-dimethyl ether gave diacetylphloroglucinol 1 : 5-dimethyl ether (I; R = Me) along with a little diacetylphloroglucinol 1-methyl ether (III; R = Me). Under the usual conditions the same mixture was obtained unexpectedly from phloracetophenone 2 : 6-dimethyl ether, implying the migration of an acetyl group. This was supported by the observation that, on treatment with boron trifluoride in a small quantity of acetic acid, phloracetophenone 2 : 6-dimethyl ether gave a little phloracetophenone 2 : 4-dimethyl ether and, possibly, some *O*-dimethylphloroglucinol, a finding which may also explain the difference in the results obtained with the Hoesch and boron trifluoride procedures. Although phloroglucinol diethyl ether gave a mixture of diacetylphloroglucinol 1 : 5-diethyl (I; R = Et) and 1-ethyl ether (III; R = Et), phloracetophenone 2 : 6-diethyl ether was attacked with simultaneous partial dealkylation and only diacetylphloroglucinol 1-ethyl ether could be isolated.

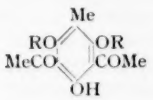
Diacetylphloroglucinol 1 : 3-dimethyl ether (II; R = H) was subsequently prepared and on treatment with free boron trifluoride isomerised completely to diacetylphloroglucinol 1 : 5-dimethyl ether (I; R = Me), whilst with boron trifluoride etherate in the absence of free boron trifluoride the *C*-acetyl group in the *p*-position to the hydroxyl group was eliminated, giving phloracetophenone 2 : 4-dimethyl ether.

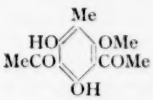


The orientation of diacetylphloroglucinol 1-methyl ether (III; R = Me) follows on general grounds from its formation by the controlled methylation of diacetylphloroglucinol which, under somewhat more drastic conditions, gives the 1 : 5-dimethyl ether (I; R = Me) of known orientation. Partial benzylation of diacetylphloroglucinol furnished the 1-benzyl ether (III; R = CH_2Ph), having the expected positive indophenol reaction, and, on methylation followed by debenzylation of the resulting mixed ether (II; R = CH_2Ph), this compound was converted into a dimethyl ether of diacetylphloroglucinol which is isomeric with the known 1 : 5-dimethyl ether (I; R = Me) and is, therefore, diacetylphloroglucinol 1 : 3-dimethyl ether (II; R = H). Similarly, the dibenzyl ether of diacetylphloroglucinol is, by analogy with (I; R = Me), the 1 : 5-dibenzyl derivative (I; R = CH_2Ph) and on methylation gives diacetylphloroglucinol 1 : 5-dibenzyl 3-methyl ether (IV; R = CH_2Ph) which, on debenzylation, furnished diacetylphloroglucinol 3-methyl ether (IV; R = H), forming diacetylphloroglucinol trimethyl ether on methylation. In agree-

ment with the orientations allotted to the monomethyl ethers (III; R = Me) and (IV; R = H) the compound (III; R = Me) gives a positive indophenol reaction whereas (IV; R = H) does not. Further, partial methylation of diacetylphloroglucinol 1-benzyl ether (III; R = CH_2Ph) gave diacetylphloroglucinol 1-benzyl 5-methyl ether (V) which on debenzylation yielded diacetylphloroglucinol 1-methyl ether (III; R = Me).

C-Acetylation of *C*-methylphloroglucinol or of *C*-methyl phloracetophenone by the boron trifluoride method gave 2 : 4-diacetyl-6-methylphloroglucinol (VI; R = H) whilst an excess of the reagents furnished 2 : 4-diacetyl-6-methylphloroglucinol 1 : 5-diacetate (VI; R = Ac) which appears to be identical with the ozonolysis product obtained from decarbousnic acid by Schöpf and Ross (*Annalen*, 1941, **546**, 1).


(VI)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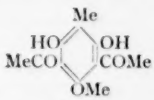
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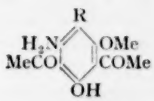

(IX)

Similarly, 2 : 4-diacetyl-6-methylphloroglucinol 1-methyl ether (VII) was obtained from *C*-methylphloroglucinol 2-methyl ether and from *C*-methylphloracetophenone 4-methyl ether and was identical with the product formed by the ozonolysis of usnetol monomethyl ether (Schöpf and Ross, *loc. cit.*), giving *C*-methylphloracetophenone 4-methyl ether on hydrolysis. The isomeride 2 : 4-diacetyl-6-methylphloroglucinol 3-methyl ether (VIII) was obtained from *C*-methylphloracetophenone 6-methyl ether only when the reaction was carried out at above 100° and can be readily distinguished from (VII) by its failure to give a monoketone on hydrolytic decomposition. On the other hand, *C*-methylphloroglucinol 2 : 4-dimethyl ether gave only *C*-methylphloracetophenone 2 : 4-dimethyl ether; a second acetyl group could not be introduced.

In attempts to deacetylate some of the acetates of the diketones with alcoholic ammonia it was found that diacetylphloroglucinol 1-methyl ether gave a nitrogenous derivative which appeared to have the empirical formula $C_{10}H_{10}O_5N{\cdot}OMe$ and to be formed by replacing a carbonyl by an imino-group or a hydroxyl by an amino-group. With a phloroglucinol derivative the latter change is more probable and at present the product is formulated as (IX; R = H). A similar compound, probably (IX; R = Me), was obtained from 2 : 4-diacetyl-6-methylphloroglucinol 1-methyl ether.

Experimental

Except where stated, the light petroleum employed had b. p. 60—80°.

2 : 4- *and* 4 : 6-*Diacetylresorcinol.*—(*a*) A stream of boron trifluoride was led into a mixture of resacetophenone (2 g.), acetic acid (3 ml.), and acetic anhydride (1·4 g.) at 80° for ½ hour, and the mixture kept at 80° for 1 hour, cooled, and diluted with ether. A solution of the resulting yellow product in the minimum volume of hot 80% alcohol was kept at 70° until the colour was discharged and then, on being cooled, gave a colourless crystalline solid (1·8 g.) which was isolated and extracted with hot light petroleum leaving a residue of 4 : 6-diacetylresorcinol. This compound formed colourless prisms (0·9 g.), m. p. 182°, from aqueous alcohol, having a red-brown ferric reaction and a negative 2 : 6-dichloroquinone chloroimide reaction (cf. Gibbs, *Chem. Reviews*, 1927, **3**, 291), and on methylation by the methyl iodide–potassium carbonate method gave the mono- and the di-methyl ether, m. p. 121·5° and 171°, respectively (cf. Eijkmann, Bergema, and Henrard, *Chem. Weekblad*, 1904, **1**, 453).

Evaporation of the light petroleum extract left 2 : 4-diacetylresorcinol, forming colourless needles (0·8 g.), m. p. 85°, from dilute alcohol, which gave an intense red ferric and a mauve 2 : 6-dichloroquinone chloroimide reaction, and a green colour with dilute alkaline hydrogen peroxide.

(*b*) By the interaction of resorcinol dimethyl ether, acetyl chloride, and aluminium chloride Mauthner (*J. pr. Chem.*, 1928, **119**, 311) obtained 4 : 6-resodiacetophenone monomethyl and dimethyl ether. Repetition of this gave the following results. The product from the interaction of resorcinol dimethyl ether (18 g.), acetyl chloride (21 g.), and aluminium chloride (40 g.) in carbon disulphide (30 ml.) at 10° for 1 hour, followed by evaporation of the solvent on the

water-bath, was decomposed with ice and concentrated hydrochloric acid. After being washed with dilute hydrochloric acid, the precipitate was extracted with 2N-sodium hydroxide (100 ml.), and the insoluble residue crystallised from 80% acetic acid, giving the dimethyl ether, m. p. 171°, of 4 : 6-diacetylresorcinol (0·4 g.). The solid from the acidified alkaline extract was digested with hot light petroleum and then crystallised from 80% acetic acid, yielding 4 : 6-diacetylresorcinol (2·3 g.), m. p. 183°. The light petroleum extract contained 4 : 6-diacetylresorcinol monomethyl ether (0·7 g.), m. p. 120°, and a more soluble product which separated from 80% acetic acid in faintly yellow prisms (1·6 g.), m. p. 137°, soluble in aqueous sodium hydrogen carbonate and having a brown-red ferric reaction (Found, in specimen dried in a high vacuum at 80° : C, 61·2; H, 5·4; MeO, 0. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). This compound appears to be 2 : 4 : 6-*triacetylresorcinol*; it was not attacked by 2N-sodium hydroxide at 100° for 4 hours, reacted with 2 : 4-dinitrophenylhydrazine, and gave a green colour with alkaline hydrogen peroxide. In the purification of the monomethyl ether of 4 : 6-diacetylresorcinol by crystallisation alternately from dilute alcohol and light petroleum a more soluble product, m. p. 109°, was obtained which, since on methylation it gave only the dimethyl ether of 4 : 6-resodiacetophenone, appeared to be a eutectic mixture of 4 : 6-diacetylresorcinol and its monomethyl ether in the ratio approximately 1 : 6. A mixture of the two compounds in this proportion had the same m. p. and mixed m. p. 109°, and was unchanged on repeated recrystallisation from a variety of solvents.

Ethers of 2 : 4-*Diacetylresorcinol.*—(*a*) Methylation of 2 : 4-diacetylresorcinol (2 g.) with methyl sulphate (1·3 g.) and potassium carbonate (1·3 g.) in boiling acetone (100 ml.) for 2 hours gave 2 : 4-*diacetyl*-1-O-*methylresorcinol*, forming large prisms (1·1 g.), m. p. 104°, from light petroleum, which had a deep red ferric reaction (Found, in specimen dried in a high vacuum at 60° : C, 63·7; H, 5·6; OMe, 15·3. $C_{10}H_9O_3{\cdot}OMe$ requires C, 63·5; H, 5·8; OMe, 14·9%). The following alternative preparation served to establish the orientation of this compound : A mixture of 2-hydroxy-4-methoxyacetophenone (3 g.), acetic anhydride (1·6 ml.), and acetic acid (5 ml.) was saturated with boron trifluoride at 50°, kept for 1 hour, and treated with ether (100 ml.). Decomposition of the yellow precipitate with aqueous alcohol gave unchanged ketone but on acidification an N-sodium hydroxide extract of the ethereal filtrate gave 2 : 4-diacetyl-1-*O*-methylresorcinol, m. p. 104° after purification, which did not give a colour with 2 : 6-dichloroquinone chloroimide, a property now found to be common to *o*-hydroxy-aldehydes and -ketones.

Methylation of 2 : 4-diacetyl-1-*O*-methylresorcinol (0·5 g.) with methyl sulphate (0·3 ml.) and potassium carbonate (0·35 g.) in boiling acetone (150 ml.) for 3 hours furnished 2 : 4-*diacetylresorcinol dimethyl ether* which separated from ether and then light petroleum in prisms (0·3 g.), m. p. 60—63°, with a negative ferric reaction [Found : C, 64·7; H, 6·5; OMe, 27·9. $C_{10}H_8O_2(OMe)_2$ requires C, 64·9; H, 6·4; OMe, 27·9%].

(*b*) On being heated under reflux for 8 hours a mixture of 2 : 4-diacetylresorcinol (6 g.), potassium carbonate (6 g.), benzyl bromide (3·8 ml.), and acetone (100 ml.) containing a trace of potassium iodide gave 2 : 4-*diacetyl*-1-O-*benzylresorcinol*, isolated from a benzene solution of the crude product with 2N-sodium hydroxide. Crystallised from benzene–light petroleum, this ether formed colourless prisms (1·8 g.), m. p. 92°, having a deep red ferric reaction (Found, in specimen dried in a high vacuum at 60° : C, 70·7; H, 5·4. $C_{17}H_{16}O_4$ requires C, 70·2; H, 5·7%). After the removal of this compound evaporation of the benzene liquors left 2 : 4-*diacetylresorcinol dibenzyl ether* which separated from benzene–light petroleum and then aqueous alcohol in colourless prisms (3·8 g.), m. p. 128—129°, with a negative ferric reaction (Found, in specimen dried in a high vacuum at 80° : C, 77·3; H, 5·9. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%). Methylation of the monobenzyl ether (0·9 g.) by the methyl iodide–potassium carbonate method yielded 2 : 4-*diacetyl*-1-O-*benzyl*-3-O-*methylresorcinol*, separating from benzene–light petroleum in prisms (0·8 g.), m. p. 101°, with a negative ferric reaction (Found : C, 72·4; H, 6·3; OMe, 10·0. $C_{17}H_{15}O_3{\cdot}OMe$ requires C, 72·5; H, 6·1; OMe, 10·4%).

Phloracetophenone 2 : 4-*Dimethyl Ether.*—(*a*) A solution of phloroglucinol dimethyl ether (5 g.) in ether (10 ml.), containing acetic anhydride (3·5 g.), was saturated with boron trifluoride at 15° and an hour later a yellow solid was isolated by precipitation with water. On decomposition with aqueous alcohol followed by distillation with steam this furnished phloracetophenone 2 : 4-dimethyl ether (3·1 g.), m. p. and mixed m. p. 81°, having a negative indophenol reaction. On crystallisation from alcohol the resinous residue, non-volatile in steam, gave a little phloracetophenone 2 : 6-dimethyl ether.

(*b*) A stream of boron trifluoride was led into phloracetophenone 2 : 6-dimethyl ether (0·5 g.) dissolved in boron trifluoride–ether complex (20 ml.) for 15 min. and next day the mixture was

treated with water (100 ml.). After the removal of the ether with a current of air the solid was decomposed with steam, giving a small amount of phloracetophenone 2 : 4-dimethyl ether, m. p. and mixed m. p. 188°, in the distillate (cf. Canter *et al.*, *loc. cit.*, who give m. p. 185·5°). Crystallised from alcohol, the non-volatile residue gave unchanged phloracetophenone 2 : 6-dimethyl ether (0·3 g.).

(*c*) Interaction of boron fluoride–ether complex (20 ml.), diacetylphloroglucinol 1 : 3-dimethyl ether (0·5 g.), and acetic acid (2 ml.) for 24 hours with isolation of the product in the usual manner gave phloracetophenone 2 : 4-dimethyl ether (0·25 g.), m. p. and mixed m. p. 81·5°.

Phloracetophenone 2 : 4- *and* 2 : 6-*Diethyl Ether*.—Interaction of phloroglucinol diethyl ether (Robertson and Subramaniam, *J.*, 1937, 286) (5 g.), methyl cyanide (8 ml.), zinc chloride (5 g.), and excess of hydrogen chloride in ether (200 ml.) at 0° gave a crystalline solid which was isolated next day and dissolved in cold water (150 ml.). The precipitate, which separated almost immediately, was warmed with N-sodium hydroxide (120 ml.) until the evolution of ammonia had ceased and on acidification the resulting solution gave a mixture of the ketones which was crystallised from a little 80% alcohol (yield, 3·2 g.). Extraction of this product with hot light petroleum left a residue of *phloracetophenone* 2 : 6-*diethyl ether* which separated from dilute alcohol in colourless plates (1·8 g.), m. p. 186—187°, with a negative ferric or indophenol reaction [Found, in specimen dried in a vacuum at 80° : C, 64·1; H, 7·0; OEt, 39·4. $C_8H_6O_2(OEt)_2$ requires C, 64·3; H, 7·2; OEt, 40·2%]. Evaporation of the light petroleum extract left phloracetophenone 2 : 4-diethyl ether (Kostanecki and Tambor, *Ber.*, 1899, **32**, 2263) forming colourless needles (1·1 g.), m. p. 85°, from dilute alcohol, with a plum-red ferric and a blue 2 : 6-dichloroquinone chloroimide reaction.

The isomeric diethyl ethers were methylated by the methyl iodide–potassium carbonate method, giving, respectively, *phloracetophenone* 2 : 6-*diethyl* 4-*methyl ether* which formed large plates, m. p. 83°, from light petroleum (Found : C, 65·8; H, 7·7. $C_{13}H_{18}O_4$ requires C, 65·6; H, 7·6%) and *phloracetophenone* 2 : 4-*diethyl* 6-*methyl ether* as an oil, b. p. 135°/0·05 mm. (Found : C, 65·6; H, 7·4%).

Diacetylphloroglucinol (I; R = H).—Interaction of phloroglucinol (3 g.), acetic anhydride (5 g.), and excess of boron trifluoride in ether (30 ml.) at 20°, followed an hour later by removal of the solvent with air, gave a boron fluoride complex which was washed with water and dissolved in hot 80% alcohol. On cooling, the solution deposited the diketone in prisms (4 g.), m. p. 168°, after sublimation in a high vacuum or recrystallisation from benzene–light petroleum (Found, in specimen dried in a high vacuum at 80° : C, 57·0; H, 4·8. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%). This compound is soluble in aqueous sodium hydrogen carbonate or benzene and gives an intense red ferric reaction in alcohol. Prepared by the pyridine method, the O-*tribenzoate* separated from benzene in large colourless prisms, m. p. 137°, with a negative ferric reaction (Found : C, 71·5; H, 4·3. $C_{31}H_{22}O_8$ requires C, 71·3; H, 4·3%). The O-*triacetate* was prepared by acetic anhydride–pyridine and to prevent hydrolysis was isolated immediately on decomposition of the excess of anhydride with water. Crystallised from dilute alcohol, the compound formed colourless needles, m. p. 92—93°, with a negative ferric reaction (Found : C, 57·3; H, 4·8. $C_{16}H_{16}O_8$ requires C, 57·1; H, 4·8%). When the aqueous reaction mixture was kept for 24 hours the product consisted of 2 : 4-*diacetylphloroglucinol* 1 : 5-*diacetate* (I; R = Ac) which was also formed by partial hydrolysis of the triacetate (1·7 g.) with pyridine (10 ml.) containing water (0·1 ml.) for 24 hours. This derivative separated from aqueous alcohol in colourless needles, m. p. 116°, with a deep red ferric reaction (Found : C, 57·2; H, 5·1. $C_{14}H_{14}O_7$ requires C, 57·1; H, 4·8%).

2 : 4-*Diacetylphloroglucinol* 1-*Methyl Ether* (III; R = Me).—A mixture of phloroglucinol monomethyl ether (1 g.), acetic acid (2 ml.), acetic anhydride (1·4 g.), and an excess of boron trifluoride were kept for 1 hour at 20° and diluted with excess of ether. On being cooled, a solution of the resulting solid in hot 60% alcohol deposited 2 : 4-*diacetylphloroglucinol* 1-*methyl ether* in needles (1·3 g.), m. p. 106°, unchanged on repeated purification and identical with a specimen prepared from diazomethane and diacetylphloroglucinol in benzene or by methylation of diacetylphloroglucinol (1 g.) with methyl iodide (2 ml.) and potassium acetate (4 g.) in boiling acetone (100 ml.) for 3 hours (Found, in a specimen dried in a high vacuum at 60° : C, 58·8; H, 5·3; OMe, 13·5. $C_{10}H_9O_4{\cdot}OMe$ requires C, 58·9; H, 5·4; OMe, 13·8%). This ether is soluble in aqueous sodium hydrogen carbonate, warm light petroleum, and the usual organic solvents, and gives an intense dark red ferric reaction and a purple colour with 2 : 6-dichloroquinone chloroimide. Prepared by the pyridine method, the *dibenzoate* formed colourless prisms, m. p. 120·5°, from benzene–light petroleum, with a negative ferric reaction (Found : C, 69·7; H, 4·7; OMe, 7·3. $C_{24}H_{17}O_6{\cdot}OMe$ requires C, 69·5; H, 4·7; OMe, 7·2%).

Diacetylphloroglucinol 1-methyl ether (0·5 g.), methyl sulphate (1 ml.), and potassium carbonate (2 g.) in boiling acetone (50 ml.) (2 hours) gave 2 : 4-*diacetylphloroglucinol* 1 : 3 : 5-*trimethyl ether*, prisms (0·5 g.) (from light petroleum), m. p. 110—111°, with a negative ferric reaction [Found : C, 62·2; H, 6·3; OMe, 36·8. $C_{10}H_7O_2(OMe)_3$ requires C, 61·9; H, 6·4; OMe, 36·9%].

Benzylation of diacetylphloroglucinol 1-methyl ether by the potassium carbonate–acetone method yielded 2 : 4-*diacetylphloroglucinol* 3 : 5-*dibenzyl* 1-*methyl ether*, forming plates, m. p. 131°, from benzene–light petroleum (Found : C, 74·1; H, 6·2; OMe, 7·4. $C_{24}H_{21}O_4{\cdot}OMe$ requires C, 74·3; H, 6·0; OMe, 7·9%). Hydrogenolysis of this in methanol with hydrogen and palladium–charcoal regenerated the parent 1-methyl ether.

Diacetylphloroglucinol 1-*Benzyl Ether* (III; R = CH_2Ph).—Diacetylphloroglucinol (4 g.), benzyl bromide (2·7 ml.), potassium carbonate (2·5 g.), a trace of potassium iodide, and acetone (250 ml.) were heated under reflux for 3 hours. The 1-*benzyl ether* crystallised from 90% alcohol in colourless silky needles (2·0 g.), m. p. 127°, with a red ferric reaction and a purple 2 : 6-dichloroquinone chloroimide reaction (Found, in specimen dried in a high vacuum at 80° : C, 68·1; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). This was accompanied by unchanged diacetylphloroglucinol (0·2 g.) and an alkali-soluble oil (1·3 g.) which was purified by way of its copper derivative, followed by distillation in a vacuum (b. p. 200°/0·3 mm.) (Found : C, 72·3; H, 5·5%), and had a dark red ferric reaction. Debenzylation of the 1-benzyl ether with hydrogen at 40 lb./sq. in. and palladium–charcoal regenerated diacetylphloroglucinol, m. p. and mixed m. p. 168°.

Methylation of diacetylphloroglucinol 1-benzyl ether (2 g.) with methyl sulphate (1 g.) and potassium carbonate (1 g.) in boiling acetone (100 ml.) for 4 hours gave *diacetylphloroglucinol* 1-*benzyl* 5-*methyl ether* (V), prisms (1·5 g.), m. p. 95°, from benzene–light petroleum, with a blood-red ferric reaction (Found : C, 69·1; H, 5·9; OMe, 9·0. $C_{17}H_{15}O_4{\cdot}OMe$ requires C, 68·8; H, 5·8; OMe, 9·9%). Hydrogenolysis of this gave phlorodiacetophenone 1-methyl ether, m. p. and mixed m. p. 106°.

Treatment of diacetylphloroglucinol 1-benzyl ether (1 g.) with an excess of methyl iodide and potassium carbonate in boiling acetone (60 ml.) for 8 hours gave *diacetylphloroglucinol* 1-*benzyl* 2 : 5-*dimethyl ether* (II; R = CH_2Ph), prisms (1·1 g.), m. p. 84—85°, from light petroleum [Found : C, 69·6; H, 6·3; OMe, 19·4. $C_{17}H_{14}O_3(OMe)_2$ requires C, 69·5; H, 6·2; OMe, 19·0%]. On debenzylation this compound (1 g.) gave *diacetylphloroglucinol* 1 : 3-*dimethyl ether* (II; R = H) which separated from dilute alcohol or light petroleum in prisms (0·6 g.), m. p. 106°, with a deep red ferric reaction [Found : C, 60·5; H, 6·0; OMe, 26·1. $C_{10}H_8O_3(OMe)_2$ requires C, 60·5; H, 5·9; OMe, 26·1%]. Methylation of this furnished diacetylphloroglucinol trimethyl ether, m. p. and mixed m. p. 110°.

Diacetylphloroglucinol 1 : 5-*Dimethyl Ether* (I; R = Me).—Interaction of phloroglucinol dimethyl ether (2 g.) with acetic acid (2 ml.), acetic anhydride (2·4 g.), and an excess of boron trifluoride at 10° for an hour followed by dilution with ether (100 ml.) gave a yellow solid, decomposing with hot 50% alcohol to diacetylphloroglucinol 1 : 5-dimethyl ether which separated from the cooled solution and then crystallised from light petroleum in colourless needles (2 g.), m. p. 128°, with an intense red ferric reaction, readily soluble in the usual organic solvents, and insoluble in aqueous sodium hydrogen carbonate [Found : C, 60·4; H, 5·8; OMe, 25·2. Calc. for $C_{10}H_8O_3(OMe)_2$: C, 60·5; H, 5·9; OMe, 26·1%] (cf. Gruber and Traub, *loc. cit.*). This ether, which had a negative 2 : 6-dichloroquinone chloroimide reaction, was accompanied by a small amount of diacetylphloroglucinol 1-methyl ether, m. p. and mixed m. p. 105°. When phloroglucinol dimethyl ether was replaced by phloracetophenone 2 : 4- or 2 : 6-dimethyl ether and one mol. of acetic anhydride was employed the same products were obtained. The acetate of diacetylphloroglucinol 1 : 5-dimethyl ether had m. p. 152° (Found : C, 59·9; H, 6·0. Calc. for $C_{14}H_{16}O_6$: C, 60·0; H, 5·8%) (cf. Tutin and Caton, *loc. cit.*).

A solution of diacetylphloroglucinol 1 : 3-dimethyl ether (0·5 g.) in ether (20 ml.) containing a little acetic acid was saturated with boron trifluoride and on isolation next day the product was separated into diacetylphloroglucinol 1-methyl ether (less soluble product) (0·05 g.), m. p. and mixed m. p. 105°, and diacetylphloroglucinol 1 : 5-dimethyl ether (0·2 g.), m. p. and mixed m. p. 128°, by fractional crystallisation from dilute alcohol.

Diacetylphloroglucinol 1 : 5-dimethyl ether, m. p. and mixed m. p. 128°, was also prepared by methylation of diacetylphloroglucinol (1 g.) with methyl iodide (2 ml.) and potassium carbonate (2 g.) in boiling acetone (50 ml.) for 2 hours.

Ethylation of diacetylphloroglucinol 1 : 5-dimethyl ether with excess of ethyl iodide by the potassium carbonate–acetone method gave *diacetylphloroglucinol* 3-*ethyl* 1 : 5-*dimethyl ether*,

prisms (from light petroleum), m. p. 96° (Found: C, 63·6; H, 7·0. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

Benzylation of diacetylphloroglucinol 1 : 5-dimethyl ether by the usual method for 16 hours gave *diacetylphloroglucinol 3-benzyl 1 : 5-dimethyl ether* which crystallised from light petroleum in thick irregular prisms, m. p. 122° [Found: C, 69·4; H, 6·1; OMe, 18·7. $C_{17}H_{14}O_3(OMe)_2$ requires C, 69·5; H, 6·2; OMe, 19·0%]. Hydrogenolysis of this regenerated the parent dimethyl ether.

Diacetylphloroglucinol 1-Ethyl and 1 : 5-Diethyl Ether.—A solution of phloroglucinol diethyl ether (2 g.) in acetic acid (2 ml.) and acetic anhydride (2·2 g.) was treated with an excess of boron trifluoride at 10—15° for 24 hours. Precipitated with ether (70 ml.) and decomposed with hot dilute alcohol, the yellow product furnished *diacetylphloroglucinol 1 : 5-diethyl ether*, forming irregular prisms (0·8 g.), m. p. 117°, from light petroleum with a red-brown ferric reaction [Found: C, 63·1; H, 4·9; OEt, 33·4. $C_{10}H_8O_3(OEt)_2$ requires C, 63·2; H, 4·9; OEt, 33·8%]. After the separation of the yellow solid the ethereal filtrate was mixed with water, the ether evaporated, and the resulting solid crystallised from light petroleum, giving *diacetylphloroglucinol 1-ethyl ether* in plates (0·4 g.), m. p. 131—131·5°, with a cherry-red ferric and a purple indophenol reaction (Found: C, 60·4; H, 5·9; OEt, 18·6. $C_{10}H_9O_4{\cdot}OEt$ requires C, 60·5; H, 5·9; OEt, 18·9%).

A mixture of ether (5 ml.) and acetic anhydride (0·3 g.) containing a suspension of phloracetophenone 2 : 6-diethyl ether (0·6 g.) was saturated at below 0° with a slow stream of boron trifluoride and immediately treated with ether (100 ml.) and water (100 ml.), with subsequent evaporation of the ether. On decomposition, the resulting complex furnished only diacetylphloroglucinol 1-ethyl ether, m. p. and mixed m. p. 131°.

Methylated with methyl sulphate by the potassium carbonate–acetone method, diacetylphloroglucinol 1-ethyl ether gave *diacetylphloroglucinol 1-ethyl 3 : 5-dimethyl ether* which separated from light petroleum in flat needles, m. p. 63° (Found: C, 63·4; H, 7·1. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). Similarly diacetylphloroglucinol 1 : 5-diethyl ether gave *diacetylphloroglucinol 1 : 5-diethyl 3-methyl ether*, plates, m. p. 107° (from light petroleum) (Found: C, 64·2; H, 7·0. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%). The isomeride *diacetylphloroglucinol 1 : 3-diethyl 5-methyl ether* was prepared from diacetylphloroglucinol 1-methyl ether with ethyl sulphate or iodide and formed prisms, m. p. 79—80°, from light petroleum (Found: C, 64·2; H, 7·2%).

Diacetylphloroglucinol 1 : 5-Dibenzyl Ether.—Etherification of diacetylphloroglucinol 1-benzyl ether (3 g.) with benzyl bromide (1·3 ml.), potassium carbonate (1·4 g.), and a trace of potassium iodide in boiling acetone (150 ml.) for 8 hours gave the *1 : 5-dibenzyl ether* which separated from dilute alcohol and then light petroleum–benzene in plates (2·9 g.), m. p. 112°, with a brown-red ferric reaction (Found, in specimen dried in a high vacuum at 60°: C, 74·1; H, 6·1. $C_{24}H_{22}O_5$ requires C, 73·9; H, 5·7%). Methylated by the methyl iodide–potassium carbonate method, this compound gave *diacetylphloroglucinol 1 : 5-dibenzyl 3-methyl ether*, prisms, m. p. 93°, from benzene–light petroleum and then dilute alcohol (Found: C, 74·0; H, 6·1. $C_{25}H_{24}O_5$ requires C, 74·2; H, 5·9%). Debenzylation of this gave *diacetylphloroglucinol 3-methyl ether*, crystallising from 40% alcohol in pale fawn, irregular leaflets, m. p. 88°, with a red ferric reaction (Found, in a specimen dried in a high vacuum at 60°: C, 58·5; H, 5·5; OMe, 13·5. $C_{10}H_9O_2{\cdot}OMe$ requires C, 58·9; H, 5·4; OMe, 13·8%). On methylation the 3-methyl ether gave phlorodiacetophenone trimethyl ether, m. p. and mixed m. p. 107°. Ethylation gave phlorodiacetophenone 4 : 6-diethyl 2-methyl ether, m. p. and mixed m. p. 107°. The solid (0·5 g.) obtained by acetylation of diacetylphloroglucinol 3-methyl ether (0·5 g.) with acetic anhydride (6 ml.) and a trace of pyridine was well washed and dried. Crystallised from light petroleum, this gave *diacetylphloroglucinol 1 : 5-diacetate 3-methyl ether* in flat prisms, m. p. 99—100°, with a negative ferric reaction (Found: C, 58·5; H, 5·5; OMe, 8·9. $C_{14}H_{13}O_6{\cdot}OMe$ requires C, 58·4; H, 5·3; OMe, 10·1%).

Triacetylphloroglucinol.—A mixture of phloroglucinol (5 g.), acetic acid (5 ml.), and acetic anhydride (15 g.) was rapidly saturated with boron trifluoride without external cooling. Precipitated with water, the resulting complex was decomposed with hot 80% alcohol, giving *triacetylphloroglucinol* in pale cream-coloured needles (6 g.), m. p. 156°, with an intense dark red ferric reaction and giving an intense green colour with alkaline hydrogen peroxide (Found, in a specimen dried in a high vacuum at 80°: C, 57·1; H, 5·1. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%). Prepared by the methyl sulphate–potassium carbonate method, the *trimethyl ether* crystallised from dilute alcohol in colourless prisms, m. p. 122—124° [Found: C, 61·2; H, 6·1; OMe, 29·2. $C_{12}H_9O_3(OMe)_3$ requires C, 61·2; H, 6·2; OMe, 31·6%].

C-Methylphloracetophenone **4 : 6-***Dimethyl Ether.*—Interaction of *C*-methylphloroglucinol **2 : 4**-dimethyl ether (**2** g.) with acetic acid (**5** ml.), acetic anhydride (**3** g.), and excess of boron trifluoride at **20—30°**, followed by decomposition of the product with hot **70%** alcohol, gave *C*-methylphloracetophenone **4 : 6**-dimethyl ether, forming faintly yellow prisms (**1·5** g.), m. p. **145°**, from alcohol with a brownish-red ferric and a negative indophenol reaction, identical with an authentic specimen (cf. Curd and Robertson, Part I, *J.*, **1933**, 437, who give m. p. **141—142°**). Replacement of *C*-methylphloroglucinol **2 : 4**-dimethyl ether with the trimethyl ether gave the same product when the reaction was carried out at **20—30°** or at **100°**.

2 : 4-*Diacetyl-6-methylphloroglucinol.*—A mixture of *C*-methylphloroglucinol (**1** g.), acetic acid (**10** ml.), acetic anhydride (**1·5** g., **2** mol.), and excess of boron trifluoride was kept at room temperature for **20** hours and treated with water. Decomposition of the resulting solid with hot **80%** alcohol yielded **2 : 4**-diacetyl-6-methylphloroglucinol, forming colourless needles (**0·9** g.), m. p. **160°**, from dilute alcohol or on sublimation in a high vacuum (Found, in a specimen dried in a high vacuum at **80°** : C, **58·8**; H, **5·6**. Calc. for $C_{11}H_{12}O_5$: C, **58·9**; H, **5·4%**). With an excess of acetic anhydride the product consisted of **2 : 4**-diacetyl-6-methylphloroglucinol **1 : 5**-diacetate which separated from light petroleum in needles, m. p. **116°**, with an intense red ferric and a negative indophenol reaction (Found : C, **58·2**; H, **4·9**. Calc. for $C_{15}H_{16}O_7$: C, **58·4**; H, **5·2%**). The orientation of this compound follows from its production by ozonolysis of decarbousnic acid (cf. Schöpf and Ross., *loc. cit.*).

Methylated by the methyl sulphate–potassium carbonate method in boiling acetone for **2** hours, **2 : 4**-diacetyl-6-methylphloroglucinol gave an almost quantitative yield of the *trimethyl ether*, separating from light petroleum (b. p. **40—60°**) in colourless prisms, m. p. **66—67°**, insoluble in aqueous sodium hydroxide and with a negative ferric reaction [Found : C, **63·1**; H, **7·0**; OMe, **35·0**. $C_{11}H_9O_2(OMe)_3$ requires C, **63·2**; H, **6·9**; OMe, **35·0%**].

Acetylation of **2 : 4**-diacetyl-6-methylphloroglucinol (**0·5** g. of anhydrous compound) with acetic anhydride (**17** ml.) and sodium acetate (**3** g.) for **3** days at room temperature gave the triacetate, isolated by evaporation of the filtered reaction mixture and crystallised from dilute methanol as colourless plates (**0·5** g.), m. p. **86°**, with a negative ferric reaction. The same compound was formed on addition of a drop of pyridine to the diketone (**1** g.) in acetic anhydride (**10** ml.) followed by water **24** hours later. The mixture was then cooled to **0°** and on being agitated gave an almost quantitative yield of the triacetate which, on recrystallisation from dilute alcohol, had m. p. and mixed m. p. **86—87°** (Found : C, **58·1**; H, **5·1**. Calc. for $C_{17}H_{18}O_8$: C, **58·3**; H, **5·2%**). When the aqueous solution was kept according to Schöpf and Ross (*loc. cit.*) **2 : 4**-diacetyl-6-methylphloroglucinol **1 : 5**-diacetate was obtained instead and formed colourless needles (**1** g.), m. p. and mixed m. p. **116°**, from dilute alcohol.

When water (**0·4** ml.) was added to a solution of the triacetate (**2·5** g.) in pyridine (**10** ml.), crystalline **2 : 4**-diacetyl-6-methylphloroglucinol **1 : 5**-diacetate, m. p. and mixed m. p. **116°**, gradually separated. The ready hydrolysis of the triacetate in this manner serves to explain the failure of Schöpf and Ross (*loc. cit.*) to obtain the compound by the pyridine–acetic anhydride method under the conditions employed to isolate the product. Methylation of this diacetate (**1·7** g.) with methyl iodide (**3** ml.) and potassium carbonate (**1·5** g.) in boiling acetone (**50** ml.) for **4** hours gave an oil which was dissolved in ether and washed with aqueous sodium hydroxide and then water. The residue left on evaporation of the dried ethereal solution was crystallised from light petroleum, giving **2 : 4-***diacetyl-6-methylphloroglucinol* **5-***acetate* **1 : 3-***dimethyl ether* in colourless thick leaflets (**0·8** g.), m. p. **79—80°**, with a negative ferric reaction [Found : C, **59·0**; H, **6·1**; OMe, **19·9**. $C_{13}H_{12}O_4(OMe)_2$ requires C, **58·8**; H, **5·9**; OMe, **20·2%**]. On deacetylation with **10%** hydrochloric acid (**6** ml.) in alcohol (**10** ml.) for **8** hours, this product gave *C*-methylphloracetophenone **4 : 6**-dimethyl ether, m. p. **144°**, identical with an authentic specimen, a result which serves to orient the parent compound.

2 : 4-*Diacetyl-6-methylphloroglucinol* **3-***Methyl Ether.*—A mixture of *C*-methylphloracetophenone **6**-methyl ether (**0·7** g.), acetic acid (**5** ml.), acetic anhydride (**3** ml.), and excess of boron trifluoride was kept at **80°** for **1** hour, and then heated until boron trifluoride effervesced for **20** minutes. On isolation in the usual manner **2 : 4-***diacetyl-6-methylphloroglucinol* **3-***methyl ether* was extracted from the crude product with hot light petroleum and purified from dilute alcohol, forming large flat needles (**0·4** g.), m. p. **94°**, with a brownish purple ferric and a negative indophenol reaction (Found : C, **61·0**; H, **5·9**; OMe, **14·6**. $C_{11}H_{11}O_4$·OMe requires C, **60·5**; H, **5·9**; OMe, **13·1%**). The residue, insoluble in light petroleum, consisted of a little unchanged *C*-methylphloracetophenone **6**-methyl ether. Methylated by the methyl sulphate–potassium carbonate method, **2 : 4**-diacetyl-6-methylphloroglucinol **3**-methyl ether gave **2 : 4**-diacetyl-6-methylphloroglucinol trimethyl ether, m. p. and mixed m. p. **66—67°**.

Prepared by the acetic anhydride–pyridine method, **2 : 4-*diacetyl*-6-*methylphloroglucinol* 1 : 5-*diacetate* 3-*methyl ether*** formed diamond-shaped plates, m. p. 169°, from dilute alcohol, with a negative ferric reaction (Found in sample dried in high vacuum at 80° : C, 59·9; H, 5·5. $C_{15}H_{15}O_6$·OMe requires C, 59·6; H, 5·6%).

2 : 4-*Diacetyl*-6-*methylphloroglucinol* 1-*Methyl Ether*.—(*a*) A mixture of *C*-methylphloroglucinol 2-methyl ether (2 g.), acetic anhydride (3 ml.), and excess of boron trifluoride in ether (4 ml.) was kept at 20° for 24 hours and treated with water. Decomposition of the yellow solid with hot 80% alcohol gave **2 : 4**-diacetyl-6-methylphloroglucinol 1-methyl ether in colourless needles (2·2 g.), m. p. 97°, having a rose-red ferric and a negative indophenol reaction (Found, in a specimen dried at 60° : C, 60·4; H, 6·0; OMe, 13·0. Calc. for $C_{11}H_{11}O_4$·OMe : C, 60·5; H, 5·9; OMe, 13·0%). On methylation with an excess of methyl sulphate (2·3 ml.) and potassium carbonate (0·35 g.) in boiling acetone this compound (0·6 g.) yielded **2 : 4**-diacetyl-6-methylphloroglucinol trimethyl ether, m. p. and mixed m. p. 66—67°, and a small amount of an alkali-soluble product which formed elongated prisms, m. p. 59·5—60·5°, from light petroleum or alcohol, with a purple-red ferric reaction, and is provisionally regarded as **2 : 4**-diacetyl-6-methylphloroglucinol 1 : 5-dimethyl ether. A small amount of *C*-methylphloracetophenone 4-methyl ether was isolated from the original 80% alcoholic liquors which had m. p. 195°, undepressed on admixture with authentic material, m. p. 197° (Curd and Robertson, *J.*, 1933, 1173).

A slightly improved yield of **2 : 4**-diacetyl-6-methylphloroglucinol 1-methyl ether was obtained when *C*-methylphloroglucinol 2-methyl ether was replaced by *C*-methylphloracetophenone 4-methyl ether in the boron trifluoride reaction.

(*b*) Methylation of **2 : 4**-diacetyl-6-methylphloroglucinol (1 g.) with methyl iodide or sulphate (1·25 mol.) and potassium carbonate (1 ml.) in boiling acetone (100 ml.) for 6 hours gave the 1-methyl ether which was isolated from the crude reaction product with hot light petroleum and crystallised from dilute alcohol, forming colourless needles (0·6 g.), m. p. 97°. This ether was also prepared from **2 : 4**-diacetyl-6-methylphloroglucinol with a slight excess of diazomethane in benzene and subsequent evaporation of the mixture in a vacuum. Attempts to acetylate the ether by the pyridine method failed.

When a solution of **2 : 4**-diacetyl-6-methylphloroglucinol 1-methyl ether (0·5 g.) in 2N-sodium hydroxide (25 ml.) was kept at 80° for 20 minutes and acidified, the resulting precipitate consisted of *C*-methylphloracetophenone 4-methyl ether, m. p. 198° after purification from dilute alcohol (Part I, *loc. cit.*), which had a reddish-blue ferric and a purple indophenol reaction, and by the acetic anhydride–pyridine method yielded a ***diacetate***, separating from dilute alcohol in colourless needles, m. p. 85°, with a negative ferric reaction (Found : C, 59·9; H, 5·6. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7%).

Action of Ammonia on Diacetylphloroglucinol 1-*Methyl Ether*.—On being kept the yellow solution of diacetylphloroglucinol 1-methyl ether in a little ammonia (*d* 0·880) became dark red and deposited a crystalline product. Recrystallised from dilute alcohol, the ***substance*** formed pale pink leaflets, m. p. 242°, with sintering at 240°, which had a brownish-red ferric and a deep mauve indophenol reaction (Found, in a specimen dried in a high vacuum at 80° : C, 59·3; H, 6·0; N, 6·4; OMe, 13·0. $C_{10}H_{10}O_3N$·OMe requires C, 59·2; H, 5·9; N, 6·3; OMe, 13·5%). With 1% aqueous sodium hydroxide it formed a yellow and in 10% hydrochloric acid a colourless solution. On being boiled the alkaline solution liberated ammonia.

Formed in a similar manner, the ***product*** from **2 : 4**-diacetyl-6-methylphloroglucinol 1-methyl ether separated from dilute alcohol in colourless needles, m. p. 250°, and had the same properties having a dark greenish-blue ferric and a negative indophenol reaction (Found, in a specimen dried in a high vacuum at 80° : C, 60·6; H, 6·5; N, 5·7; OMe, 13·6. $C_{11}H_{12}O_3N$·OMe requires C, 60·8; H, 6·4; N, 5·9; OMe, 13·1%).

UNIVERSITY OF LIVERPOOL. [*Received, December 29th*, 1952.]

250. *Usnic Acid. Part IX.* A Revised Structure for Usnolic Acid and the Resolution of (±)-Usnic Acid.*

By F. M. Dean, P. Halewood, S. Mongkolsuk, Alexander Robertson, and W. B. Whalley.

From 3 : 4 : 6-trimethylcoumarone (VIII; R = H) by the general method (Part VII, *J.*, 1939, 1594) an analogue (XI; R = CO_2H) of usnolic acid has been synthesised which on hydrogenation gave di- and tetra-hydro-derivatives and on ozonolysis furnished formaldehyde and a compound shown to be 3 : 4′-diketo-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid (XII; R = H). The structure of this spiran was confirmed by its conversion into 4 : 6-dimethylsalicylic acid (CO_2H = 1) on oxidation or hydrolytic fission. The position of the exocyclic methylene group attacked by ozone in the conversion of (XI; R = CO_2H) into (XII; R = H) was established by the synthesis of a homologue (XV; R = H) from 3-ethyl-4 : 6-dimethylcoumarone with subsequent ozonolysis of this homologue into acetaldehyde and the same *spiro*coumaran (XII; R = H). Similarly, methyl *O*-methylusnolate gave formaldehyde and a triketonic ester (V; R = Me, R′ = CO_2Me). On the basis of these results the structures of type (IV) have been developed for usnolic acid and its synthetical analogues described in the present work and in Part VII.

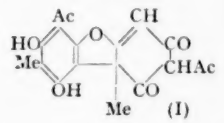
Resolution of (±)-usnic acid and a partial resolution of usnolic acid are described.

With concentrated sulphuric acid usnic acid (I) is converted into usnolic acid, an isomeric carboxylic acid, which on decarboxylation yields decarbousnol, also formed by treatment of decarbousnic acid (II; R = H) by the same reagent (Part V, *J.*, 1937, 894). After a review of the then available evidence in support of structure (I) for usnic acid, Foster, Healy, and one of us (A. R.) (Part VII, *J.*, 1939, 1594) proposed that, of the alternatives possible on the basis of formula (I) for usnic acid, usnolic acid was best represented by (III; R = CO_2H) in agreement with the structure (III; R = H) suggested for decarbousnol (Part V, *loc. cit.*), with the assumption that (III; R = CO_2H) is formed from (I) by way of (II; R = CO_2H). The synthesis of two analogues of usnolic acid, formulated as (VI; R = H, Me respectively), from intermediates of type (II; R = CO_2Et) appeared to support the furano(2′ : 3′-1 : 2)*cyclo*hexa-3 : 6-dien-5-one structure (III; R = CO_2H), especially since the synthetic compounds closely resembled usnolic acid and gave the characteristic blue colour with Ehrlich's reagent exhibited by decarbousnol but not by usnic acid or its degradation products (Part VII, *loc. cit.*). It seemed reasonably certain, therefore, that usnolic acid and its synthetic analogues were similarly constituted but experimental evidence on the nature of the ring system formed by cyclisation of substances of type (II) was lacking. In this connection it may be noted that Asahina and Okazaki (*J. Pharm. Soc. Japan*, 1943, **63**, 618; *Chem. Abs.*, 1951, **45**, 5146; † cf. *Proc. Imp. Acad. Tokyo*, 1943, **19**, 303; *Chem. Abs.*, 1947, **41**, 6235) have substantiated the work of Schöpf and Ross (*Annalen*, 1940, **546**, 1) on the ozonolysis of diacetylusnic acid supporting the structure (I) for usnic acid and by the same procedure found that decarbousnol and its diacetate gave formaldehyde and a triketone $C_{16}H_{14}O_6$. On the basis of these results and of the pyrolytic decomposition of tetrahydrodecarbousnol and the hydrogenated triketone, the Japanese workers concluded that (IV; R = R′ = H) was a possible structure for decarbousnol, apparently retaining (III; R = R′ = H) for usnolic acid and assuming (*a*) that the cyclisation of decarbousnic acid takes a different course from that occurring in the rearrangement of usnic acid to usnolic acid and (*b*) that the conversion of tetrahydrousnolic acid into tetrahydrodecarbousnol involves rearrangement in addition to de-

* Part VIII, preceding paper.

† The only account of this work available to us is the above abstract which came to hand after the greater part of the present work had been completed and the consequent conclusions developed. A. R.

carboxylation; this would presumably apply to the conversion of usnolic acid into decarbousnol.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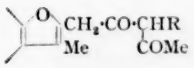
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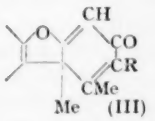
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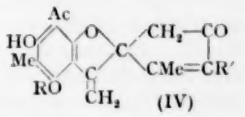
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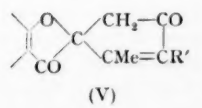
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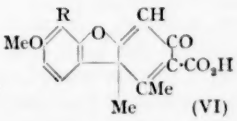
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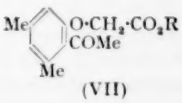
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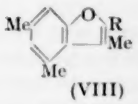
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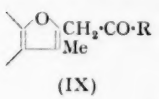
As in the case of usnolic acid the synthetic compounds (Part VII) were available to us only in small quantities and attempts have been made at various times in these laboratories (unpublished work) to provide another analogue in sufficient amount for analytical studies. In the present work, employing 3 : 4 : 6-trimethylcoumarone and effecting improved yields at several stages, we prepared the corresponding usnolic acid analogue by the general method in sufficient quantity for a detailed examination of its properties.

Prepared from 2-hydroxy-4 : 6-dimethylacetophenone, 2-acetyl-3 : 5-dimethylphenoxyacetic acid (VII; R = H) was converted into 3 : 4 : 6-trimethylcoumarone (VIII; R = H) which by Gattermann's method gave 2-formyl-3 : 4 : 6-trimethylcoumarone (VIII; R = CHO), the orientation of which was confirmed by oxidation to the carboxylic acid (VIII; R = CO_2H), identical with a specimen formed by the cyclisation of (VII; R = Et) and subsequent hydrolysis of the resulting ester (VIII; R = CO_2Et). From (VIII; R = CHO) 3 : 4 : 6-trimethylcoumarone-2-acetic acid (IX; R = OH) was prepared by the standard azlactone synthesis and converted into the acid chloride (IX; R = Cl) which reacted with the sodio- or (better) ethoxymagnesio-derivative of ethyl acetoacetate to give the diketo-ester (X). Treatment of (X) with concentrated sulphuric acid at −5° for 3 days gave the ethyl ester of the usnolic acid analogue along with a little of the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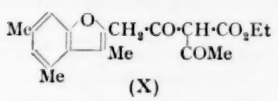
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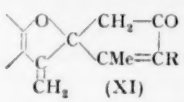
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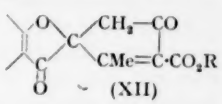
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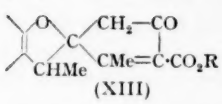
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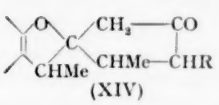
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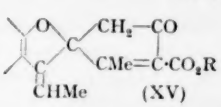
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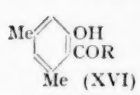
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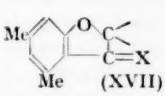
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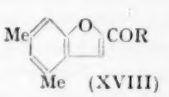
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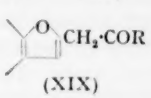
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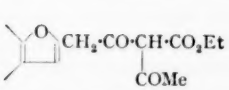
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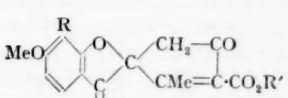
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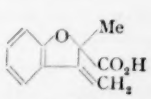
(XXII)

corresponding acid, also formed by hydrolysis of the ester; regeneration of the ester from the acid served to establish the identity of their structures. From an examination of the hydrogenation and oxidation products of this keto-acid and its ester, which give the characteristic Ehrlich reaction, it is now clear that the latter compounds do not contain the *cyclo*hexadienone system of (III) but are spirans with an exocyclic methylene group, *viz.*, 4′-keto-4 : 6 : 2′-trimethyl-3-methylene*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid (XI; R = CO_2H) and its ethyl ester. Thus, the ester, which formed a 2 : 4-dinitro-

phenylhydrazone, contained two double bonds as estimated by the perbenzoic acid method, and on hydrogenation at a palladium–charcoal catalyst gave a dihydro-derivative (XIII; R = CO_2Et) containing one double bond (perbenzoic acid method) and forming a 2 : 4-dinitrophenylhydrazone. On hydrolysis, (XIII; R = Et) gave the dihydro-acid (XIII; R = H), identical with the product formed by the hydrogenation of (XI; R = CO_2H) with the palladium catalyst. With Adams' platinum catalyst the esters (XI; R = CO_2Et) and (XIII; R = Et) gave the same tetrahydro-derivative (XIV; R = CO_2Et). Unlike the parent ester (XI; R = CO_2Et) or its dihydro-derivative (XIII; R = Et), the tetrahydro-ester (XIV; R = CO_2Et) formed an unstable dinitrophenylhydrazone and, in agreement with the keto-enolic system possible on the basis of the formula proposed, it gave a positive ferric reaction. On being kept, this compound appeared to revert completely to the keto-form since it did not then give a ferric reaction, but when heated above its melting point the resulting material again gave the ferric reaction. As expected, hydrogenation of (XI; R = CO_2H) at a platinum catalyst gave an unstable acid (XIV; R = CO_2H), having a positive ferric reaction and decomposing on recrystallisation, with the evolution of carbon dioxide, to a neutral product, undoubtedly the analogue (XIV; R = H) of tetrahydrodecarbousnol. An examination of this ketone, which was only obtained in small amounts, is reserved for a future communication.

On ozonolysis the acid (XI; R = CO_2H) and its ester (XI; R = CO_2Et) gave formaldehyde and the spirans (XII; R = H and Et respectively), which were characterised by the formation of oximes; their relationship was confirmed by esterification of (XII; R = H) with ethereal diazoethane to give a product from which the oxime of (XII; R = Et) was obtained. The product (XII; R = H) was readily oxidised by warm Fehling's solution, yielding 4 : 6-dimethylsalicylic acid (XVI; R = OH), a reaction characteristic of coumaran-3-ones; the acid (XVI; R = OH) was also formed by hydrolytic fission of (XII; R = H) with hot alkali. Clearly the conditions which lead to degradation of (XI; R = CO_2H) to (XVI; R = OH) indicate that the exocyclic methylene group in (XI; R = CO_2H) has been removed as in (XII; R = H), otherwise the ketone (XVI; R = Me), and not the acid (XVI; R = OH), would have been formed. The ultra-violet absorption curve of (XII; R = CO_2Et) are very similar to that of (XI; R = CO_2Et), apart from subsidiary variations of the latter, and suggest that the compounds contain the same fundamental system (XVII; where X = C or O). On the other hand, in agreement with the formulæ (XIII) ascribed to it and its parent acid, the dihydro-derivative does not give rise to appreciable amounts of formaldehyde on ozonolysis and does not possess the ultra-violet absorption spectrum characteristic of the system (XVII).

From the foregoing results it is evident that in the cyclisation to a spiran the 3-methyl group of the coumarone (X) becomes the methylene group of the cyclisation product (XI; R = CO_2Et). To confirm this the homologue (XV; R = Et) was synthesised by the general method. 4 : 6-Dimethylpropiophenone was converted by way of 3 : 5-dimethyl-2-propionylphenoxyacetic acid into 3-ethyl-4 : 6-dimethylcoumarone, the formyl derivative of which furnished 3-ethyl-4 : 6-dimethylcoumarone-2-acetic acid by the azlactone route. Interaction of 3-ethyl-4 : 6-dimethylcoumarone-2-acetyl chloride with the ethoxymagnesio-derivative of ethyl acetoacetate and subsequent cyclisation of the product with concentrated sulphuric acid gave a mixture of the spiran (XV; R = H) and its ethyl ester. As expected the ultra-violet absorption spectrum of this ester (XV; R = Et) was very similar to that of (XI; R = CO_2Et) and, in agreement with the view that the group >CH– in the 3-position of the furan residue is essential to spiran formation, ozonolysis of (XV; R = H or Et) gave acetaldehyde and the spiran (XII; R = H or Et respectively). In corroboration of this a small amount of the diketonic ester (XX) was synthesised by the stages (XVIII; R = OH $\longrightarrow$ Cl $\longrightarrow$ CHN_2) $\longrightarrow$ (XIX; R = $Ph{\cdot}CH_2{\cdot}O \longrightarrow OH \longrightarrow Cl$). On treatment with sulphuric acid under the usual conditions, this ester (XX) gave a neutral substance in pale yellow needles, the properties of which, including the ultra-violet absorption spectrum and negative Ehrlich reaction, differed entirely from those of (XI; R = CO_2Et) and (XV; R = H). In connection with the cyclisation of esters of type (X) it may be noted that the formation of a spiran depends on the ethylenic nature of the double bond in the furan residue (*i.e.*, its lack of aromaticity),

and the production of 2-methyl-3-methylenecoumaran-2-carboxylic acid (XXII) by carboxylation of 2-methyl-3-coumaronylmethylmagnesium chloride (Gaertner, *J. Amer. Chem. Soc.*, 1952, **74**, 5319) offers a close analogy.

From the foregoing results it is now clear that the synthetic compounds, which were formulated in Part VII as *cyclo*hexadienones of type (VI), and whose properties closely resemble those of the spirans (XI) and (XV), are the spirans (XXI; R = R′ = H, and R = Me, R′ = H) and their ethyl esters. Further, from its close similarity to the synthetic analogues usnolic acid clearly has the spiran structure (IV; R = H, R′ = CO_2H). Although, owing to its lack of solubility in suitable solvents, usnolic acid could not be oxidised with ozone, methylation with diazomethane gave the more soluble derivative, methyl O^4-methylusnolate (IV; R = Me, R′ = CO_2Me), which on ozonolysis furnished formaldehyde and a triketone. This compound, which forms a dioxime, has an ultra-violet absorption spectrum corresponding to that of a typical *C*-methylphlorodiacetophenone (Part VIII, preceding paper), and is clearly represented by formula (V; R = Me, R′ = CO_2Me). With regard to the position of the methoxyl group in (IV; R = Me, R′ = CO_2Me)

FIG. 1. FIG. 2.

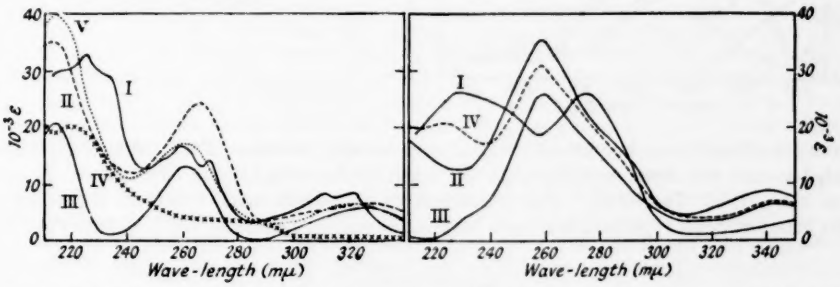

FIG. 1. I, *Ethyl* 4′-*keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Me).
II, 3 : 4′-*Diketo*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylic acid* (XII; R = H).
III, 4 : 6-*Dimethylcoumaran*-3-*one*.
IV, 4′-*Keto*-3 : 4 : 6 : 2′-*tetramethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylic acid*.
V, *Curve obtained by addition of* III *to* IV. (*All in ethanol.*)

FIG. 2. I, *Methyl* O-*methylusnolate* (IV; R = Me, R′ = CO_2Me).
II, *Methyl* 7-*acetyl*-6-*hydroxy*-3 : 4′-*diketo*-5 : 2′-*dimethyl*-4-*methoxy*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (V; R = Me, R′ = CO_2Me).
III, 2 : 4-*Diacetyl*-6-*methylphloroglucinol* 1-*methyl ether*.
IV, *Curve obtained by addition of* III *to* IV *of Fig.* 1. (*All in ethanol.*)

and its ozonolysis product it is reasonable to assume on general grounds that the phenolic hydroxyl group of usnolic acid which undergoes methylation is that in the 4-position of the coumaran residue.

The structures proposed for usnolic acid and its analogues can now be correlated with their ultra-violet absorption characteristics. In the absence of data for the unsaturated keto-acid system, the absorption of 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylic acid has been taken as an approximation to it. Addition of this absorption (Fig. 1) to that of 4 : 6-dimethylcoumaran-3-one (Fig. 1) or to that of 2 : 4-diacetyl-6-methylphloroglucinol 1-methyl ether (Fig. 2) (Part VIII) gives curves which resemble closely those of 3 : 4′-diketo-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′-*spiro*-coumaran-3′-carboxylic acid (Fig. 1) and methyl 7-acetyl-6-hydroxy-3 : 4′-diketo-4-methoxy-5 : 2′-methyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (Fig. 2) respectively. In appropriate circumstances, usnic acid can be converted into compounds containing phloracetophenone or resorcinol nuclei; therefore, the absorption curves of representative derivatives of phloracetophenone, the diacetylresorcinols, and diacetylphloroglucinol are included for comparison (see Fig. 3).

As expected on the basis of the mechanism involved for conversion (+)- or (−)-usnic

acid into usnolic acid the last compound is invariably obtained in an optically inactive state, but from the structures allocated to usnolic acid and the synthetic analogues these compounds should be resolvable. Attempts to resolve the analogue (XI; R = CO_2H) were unsuccessful but by means of the (−)-brucine salt a partial separation of usnolic acid into (+)- and (−)-fractions was effected.

Resolution of (±)-Usnic Acid.—The (+)-, (−)- and (±)-forms of usnic acid occur naturally and the comparatively ready racemisation of (+)- or (−)-usnic acid with hot

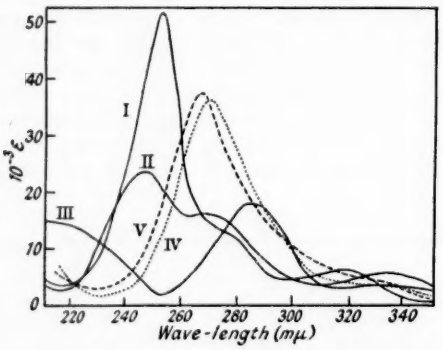

FIG. 3. I, 4 : 6-*Diacetylresorcinol.*
II, 2 : 4-*Diacetylresorcinol.*
III, 2 : 6-*Dihydroxy-4-methoxy-5-methylacetophenone.*
IV, 2 : 4-*Diacetylphloroglucinol.*
V, 2 : 4-*Diacetylphloroglucinol* 1-*methyl ether.* (*All in ethanol.*)

solvents has long been known (cf. Schöpf and Heuck, *Annalen*, 1927, **459**, 264), a result which has not yet been explained on the basis of formula (I) (cf. Mackenzie, *J. Amer. Chem. Soc.*, 1952, **74**, 4067). The resolution of (±)-usnic acid, which as far as we are aware has not been reported, has now been achieved by means of the (−)-brucine salt.

EXPERIMENTAL

Ethyl 2-Acetyl-3 : 5-dimethylphenoxyacetate (VII; R = Et).—2-Hydroxy-4 : 6-dimethylacetophenone (22·5 g.) was prepared in consistent yields by heating *m*-5-xylyl acetate (30 g.) with powdered aluminium chloride (30 g.) at 100° for 5 hours, followed by isolation in the usual manner (cf. Smith and Opie, *J. Org. Chem.*, 1941, **6**, 429; also von Auwers, *Ber.*, 1915, **48**, 90, and von Auwers and Borsche, *ibid.*, p. 1708).

A mixture of this ketone (5 g.), ethyl bromoacetate (5·5 g.), and potassium carbonate (4·7 g.) was heated in boiling acetone (50 ml.) for 20 hours. Evaporation of the filtered solution left *ethyl 2-acetyl-3 : 5-dimethylphenoxyacetate* which formed colourless needles (7·3 g.), m. p. 62°, from aqueous alcohol, readily soluble in ether or benzene, sparingly soluble in light petroleum, and having a negative ferric reaction (Found: C, 66·9; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). A mixture of this ester (146 g.), sodium hydroxide (60 g.), and 50% alcohol (600 g.) was heated on the steam-bath for 1 hour, the greater part of the solvent was distilled in a vacuum, and the residue was cooled to 0° and acidified with hydrochloric acid, giving *2-acetyl-3 : 5-dimethylphenoxyacetic acid*, which separated from dilute alcohol in needles (128 g.), m. p. 166—167° (Found: C, 64·8; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

2-Formyl-3 : 4 : 6-trimethylcoumarone (VIII; R = CHO).—A mixture of 2-acetyl-3 : 5-dimethylphenoxyacetic acid (13·5 g.), sodium acetate (25 g.), and acetic anhydride (50 ml.) was heated under reflux for 1 hour, cooled, and treated with water (300 ml.). After isolation with ether and removal of traces of acidic material with aqueous sodium hydrogen carbonate, the resulting *3 : 4 : 6-trimethylcoumarone* (VIII; R = H) formed colourless needles (8·5 g.), b. p. 128°/20 mm., m. p. 31°, from dilute acetic acid (Found: C, 80·0; H, 7·6. $C_{11}H_{12}O_2$ requires C, 80·3; H, 7·5%). When heated, the orange-red solution of this compound in concentrated sulphuric acid became in turn dark red, violet, and blue.

Condensation of 3 : 4 : 6-trimethylcoumarone (30 g.) and hydrogen cyanide (15 ml.) with aluminium chloride (28 g.) and excess of hydrogen chloride in ether (100 ml.) for 24 hours gave a crystalline product which was hydrolysed with water (2 l.) on the steam-bath for 2 hours. On being kept, the cooled hydrolysate deposited *2-formyl-3 : 4 : 6-trimethylcoumarone* (VIII; R = CHO) (30 g.) which crystallised from benzene in colourless prisms, m. p. 130—131° (Found: C, 76·6; H, 6·3. $C_{12}H_{12}O_3$ requires C, 76·5; H, 6·4%), and gave a *2 : 4-dinitrophenylhydrazone*

in small red prisms, m. p. 273°, from ethyl acetate (Found: N, 15·1. $C_{18}H_{16}O_5N_4$ requires N, 15·2%).

This aldehyde (0·5 g.), in acetone (20 ml.), was oxidised with potassium permanganate (1 g.) in water (20 ml.) for 2 hours and the solution was cleared at 0° with sulphur dioxide and diluted with water. Crystallisation of the precipitate from dilute alcohol gave 3 : 4 : 6-trimethylcoumarone-2-carboxylic acid (VIII; R = CO_2H) in colourless prisms (0·25 g.), m. p. 266—269° (decomp.) (Found: C, 70·6; H, 6·2. Calc. for $C_{12}H_{12}O_3$: C, 70·6; H, 5·9%). A mixture of this acid and its ethyl ester was formed by the cyclisation of ethyl 2-acetyl-3 : 5-dimethylphenoxyacetate (6 g.) with alcoholic sodium ethoxide (from 0·1 g. of sodium and 10 ml. of alcohol) and separated by aqueous sodium hydrogen carbonate. The acid (2·5 g.) had m. p. and mixed m. p. 266—269° (decomp.) (cf. Thorpe and Jordan, *J.*, 1915, **107**, 389, who record m. p. 149°). *Ethyl* 3 : 4 : 6-*trimethylcoumarone*-2-*carboxylate* (VIII; R = CO_2Et) formed colourless needles (2 g.), m. p. 94—95°, from dilute alcohol (Found: C, 72·3; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

3 : 4 : 6-*Trimethylcoumarone*-2-*acetic Acid* (IX; R = OH).—A mixture of 2-formyl-3 : 4 : 6-trimethylcoumarone (8 g.), hippuric acid (14 g.), sodium acetate (8 g.), and acetic anhydride (50 ml.) was heated on the steam-bath for 1½ hours and diluted with alcohol (150 ml.). Next day the crystalline *azlactone* was collected and recrystallised from acetic acid, forming orange needles (11·3 g.), m. p. 200° (Found: N, 4·3. $C_{21}H_{17}O_3N$ requires N, 4·2%). This compound (30 g.) was hydrolysed with boiling 20% aqueous potassium hydroxide (300 ml.) for 1½ hours, and the solution diluted with water (750 ml.), mixed with diatomite (5 g.), filtered, cooled, and acidified with concentrated hydrochloric acid, giving a precipitate of 3 : 4 : 5-*trimethylcoumarone*-2-*pyruvic acid* (IX; R = CO_2H) mixed with benzoic acid. When the mixture was heated to 60° on the steam-bath the benzoic acid dissolved, leaving the pyruvic acid which on isolation separated from dilute alcohol (charcoal) in pale yellow needles (17 g.), m. p. 224° (Found: C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). In the present instance this procedure for the separation of the acids was superior to the standard sulphur dioxide method.

A solution of the crude pyruvic acid (17 g.) in 10% aqueous potassium hydroxide (50 ml.) at 0° was mixed with hydrogen peroxide (20 ml. of 100 vol.), warmed until effervescence began, cooled to 0°, diluted with ice-water (1000 g.), and acidified with concentrated hydrochloric acid. Thus precipitated, 3 : 4 : 6-*trimethylcoumarone*-2-*acetic acid* (IX; R = OH) (14 g.) crystallised from dilute methanol or acetic acid in colourless plates, m. p. 186°, having a red sulphuric acid reaction (Found: C, 71·5; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

Ethyl α-*Acetyl*-γ-(3 : 4 : 6-*trimethyl*-2-*coumaronyl*)*acetoacetate* (X)—When the vigorous reaction between 3 : 4 : 6-trimethylcoumarone-2-acetic acid (5 g.) and phosphorus pentachloride (5 g.) in chloroform (50 ml.) had subsided (*ca.* 15 min.) the mixture was heated on the steam-bath for ½ hour and the solvent and phosphorus oxychloride were then removed in a vacuum, leaving the crystalline acid chloride (IX; R = Cl). With concentrated ammonia this compound gave 3 : 4 : 6-*trimethylcoumarone*-2-*acetamide* (IX; R = NH_2) which formed colourless plates, m. p. 175°, from benzene (Found: N, 6·4. $C_{13}H_{15}O_2N$ requires N, 6·5%).

Carbon tetrachloride (2 drops) was added to a hot mixture of ethyl acetoacetate (3·3 g.) and alcohol (1·2 g.) containing magnesium turnings (0·6 g.) and, after the vigorous reaction had somewhat subsided, ether (30 ml.) was introduced. The mixture was then heated under reflux until the magnesium was converted into the ethoxymagnesio-derivative of ethyl acetoacetate. This was mixed with a solution of 3 : 4 : 6-trimethylcoumarone-2-acetyl chloride (from 5 g. of acid) in ether (150 ml.) and heated for a further 6 hours, cooled, and treated with slight excess of dilute acetic acid to decompose the magnesium complex. The ethereal solution was isolated, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, leaving ethyl α-acetyl-γ-(3 : 4 : 6-trimethyl-2-coumaronyl)acetoacetate as a pale red, viscous oil (6·7 g.) with a cherry-red ferric reaction in alcohol. The same compound was prepared by the interaction of molecular proportions of the acid chloride and ethyl sodioacetoacetate in boiling ether for 24 hours. On agitation of an ethereal solution of the compound with aqueous copper acetate the green copper derivative separated.

Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—The foregoing keto-ester (5 g.) was cyclised with concentrated sulphuric acid (13 ml.) at 0° for 3 days and the dark brown mixture then poured into ice-water (50 g.). On isolation with ether the product was separated into the spiran-ester (XI; R = CO_2Et) (3 g.) and the corresponding acid (XI; R = CO_2H) (0·1 g.). The proportion of acid increased and that of its ester decreased when the reaction was carried out at higher temperatures. Similar results were obtained when the keto-ester was replaced by its sodium or

copper derivative. Purified from aqueous alcohol (charcoal) and then from light petroleum (b. p. 40—60°), the *ester* (XI; R = CO_2Et) formed colourless needles, m. p. 95—96°), moderately soluble in the usual organic solvents and giving a deep blue colour with Ehrlich's reagent and a blue colour in the Legal test (Found: C, 72·8; H, 6·2. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%). Perbenzoic acid titrations indicated the presence of 2·05 double bonds. The 2 : 4-*dinitrophenylhydrazone* separated from benzene–light petroleum (b. p. 60—80°) in orange needles, m. p. 200° (Found: N, 11·2. $C_{25}H_{24}O_7N_4$ requires N, 11·4%).

A hot solution of the ester (0·5 g.) in alcohol (8 ml.) was diluted with water to a faint turbidity at 80°, and then treated with 8% aqueous sodium hydroxide (2 ml.). 5 Minutes later the mixture was acidified with dilute hydrochloric acid and the acid was isolated with ether and purified from benzene–light petroleum (b. p. 60—80°) and then chloroform–light petroleum (b. p. 40—60°), forming pale yellow needles (0·3 g.), m. p. 166—166·5°, which give a blue Ehrlich and a red Legal test (Found: C, 71·6; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). This *acid* was identical with the product formed in the cyclisation experiments and on esterification with diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 94—95°.

During numerous attempts to resolve this acid the (+)-*N-methylamphetamine* salt was prepared by mixing solutions of the acid (3 g.) and the base (1·6 g.) in benzene. The volume of the benzene solution was reduced to about 10 ml. and, on addition of ether, the salt separated in colourless needles, m. p. 150° (Found: C, 74·7; H, 7·3; N, 3·4. $C_{17}H_{16}O_4,C_{10}H_{15}N$ requires C, 74·8; H, 7·2; N, 3·2%).

4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran* (XI; R = H).—A solution of the aforementioned acid (0·5 g.) in quinoline, containing copper bronze (0·1 g.), was kept at 190° for 10 minutes, cooled, diluted with ether (50 ml.), filtered, washed with dilute hydrochloric acid to remove the quinoline and then with aqueous sodium hydrogen carbonate, dried, and evaporated. Crystallised from light petroleum (b. p. 40—60°), the residue gave the spiro*coumaran* in almost colourless plates (0·1 g.), m. p. 80°, soluble in the usual organic solvents and giving a deep blue Ehrlich reaction (Found: C, 80·2; H, 6·8. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

Hydrogenation of Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—This ester (1 g.), in ethyl acetate (100 ml.), was hydrogenated with a palladium–charcoal catalyst (from 0·5 g. of charcoal and 2·5 ml. of 2% aqueous palladium chloride) and hydrogen at atmospheric pressure; absorption (1 mol.) was complete after ½ hour. On isolation the 3 : 4 : 6 : 2′-*tetramethyl* compound (XIII; R = Et) separated from dilute acetic acid or from light petroleum (b. p. 60—80°) in long needles (0·7 g.), m. p. 85—86°, giving a blue Ehrlich reaction (Found: C, 72·7; H, 7·1. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%); titration with perbenzoic acid indicated the presence of one double bond. The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 193—194°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·2. $C_{25}H_{26}O_7N_4$ requires N, 11·3%). An improved yield of tetramethyl compound (2·75 g. from 3 g. of ester) was subsequently obtained when the hydrogenation was effected in acetic acid, and the catalyst prepared *in situ*.

Hydrogenation of the acid (4 g.) by the same procedure gave the corresponding *acid* (XIII; R = CO_2H) which separated from dilute alcohol and then light petroleum (b. p. 60—80°) in straw-coloured, irregular plates, m. p. 139° (decomp.), having a positive Ehrlich and alkaline nitroprusside reaction and a negative ferric reaction (Found: C, 71·4; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%). The same acid was obtained by the hydrolysis of ethyl 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate by the procedure employed for the 3-methylene analogue.

With hydrogen (1 mol. absorbed) and a platinum catalyst (from 0·1 g. of platinum oxide) in ethyl acetate (50 ml.) ethyl 4′-keto-3 : 4 : 6 : 2′-tetramethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (1 g.) gave *ethyl* 4′-*keto*-3 : 4 : 6 : 2′-*tetramethyl*cyclo*pentane*-1′-spiro-2-*coumaran*-3′-*carboxylate*, forming colourless needles (0·75 g.), m. p. 91—92°, from light petroleum (b. p. 60—80°), which had a blue Ehrlich reaction and a transient ferric reaction in alcohol (freshly prepared solution) (Found: C, 72·4; H, 7·5. $C_{19}H_{24}O_4$ requires C, 72·2; H, 7·6%). It formed an unstable 2 : 4-dinitrophenylhydrazone, m. p. 99—100°, which could not be recrystallised. Hydrogenation (2 mol. of hydrogen absorbed) of the 3-methylene compound (XI; R = CO_2Et) with a platinum catalyst gave the same derivative, m. p. and mixed m. p. 91—92°.

Ozonolysis of Ethyl 4′-*Keto*-4 : 6 : 2′-*trimethyl*-3-*methylene*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* (XI; R = CO_2Et).—A stream of ozone and oxygen was led into a solution of the ester (1 g.) in carbon tetrachloride (30 ml.) until a faint turbidity appeared (35—40 min.).

After the removal of excess of ozone with a stream of oxygen the filtered solution was evaporated in a vacuum and the residual ozonide treated with water (50 ml.) for 24 hours. Distillation of the decanted aqueous liquor gave aqueous formaldehyde, identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 165°, which was purified by chromatography on aluminium oxide, and in a second experiment as the dimedone derivative (0·22 g.), m. p. 191°, identical with an authentic specimen.

The gummy residue left from the aqueous liquor was dissolved in the minimum amount of methanol and treated with 50% aqueous potassium hydroxide (15 ml.) at 0°, giving a crystalline solid (0·1—0·4 g.) which was isolated immediately, and washed with water and ether. This salt (1 g.), which had a blue ferric reaction in alcohol, was decomposed with concentrated hydrochloric acid (2 ml.) in the least quantity of 50% methanol and the resulting *ethyl* 3 : 4′-*diketo*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylate* was isolated with ether and crystallised from methanol or light petroleum, forming colourless prisms which had m. p. 91—92°, and a negative ferric and a deep green alkaline nitroprusside reaction, and reduced Fehling's solution (Found: C, 68·7; H, 6·1; OEt, 14·4. $C_{16}H_{13}O_4$·OEt requires C, 68·8; H, 5·7; OEt, 14·2%). The *oxime* separated from alcohol in flat parallelograms, m. p. 226° (decomp.), readily soluble in 2N-sodium hydroxide (yield, almost theoretical) (Found: C, 65·5; H, 5·8; OEt, 14·1. $C_{16}H_{14}O_4N$·OEt requires C, 65·7; H, 5·5; OEt, 13·7%). The same oxime was obtained from the crude resinous ozonolysis product before conversion into the potassium salt.

Similarly, ozonolysis of the acid (XI; R = CO_2H) (1 g.) in carbon tetrachloride (30 ml.) furnished formaldehyde and 3 : 4′-*diketo*-4 : 6 : 2′-*trimethyl*cyclo*pent*-2′-*ene*-1′-spiro-2-*coumaran*-3′-*carboxylic acid* which was extracted by sodium hydrogen carbonate solution from a solution of the crude ozonolysis product in ether and crystallised from benzene–light petroleum (b. p. 60—80°), forming cream-coloured hexagonal prisms (0·35 g.), m. p. 158—159° (decomp.) (Found: C, 66·6; H, 5·0. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). The *oxime* separated from dilute alcohol in cream-coloured prisms, m. p. 215° (decomp.) (Found: N, 8·8. $C_{16}H_{15}O_5N_2$ requires N, 8·9%). Esterification of the acidic ozonolysis product with ethereal diazoethane gave a gum which on oximation yielded the oxime of ethyl 3 : 4′-diketo-4 : 6 : 2′-trimethyl-*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate [m. p. and mixed m. p. 226° (decomp.)].

4 : 6-*Dimethylsalicylic Acid* (XVI; R = OH).—(*a*) Ethyl 3 : 4′-diketo-4 : 6 : 2′-trimethyl-*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (0·4 g.) was heated with Fehling's reagent (30 ml.) on the steam-bath for 20 minutes and the resulting solution acidified and extracted with ether. By means of 2N-sodium hydroxide 4 : 6-dimethylsalicylic acid (0·16 g.) was isolated from the extract and on purification from aqueous alcohol (charcoal) had m. p. 166°, identical with an authentic specimen synthesised by the following route. Prepared from 2-hydroxy-4 : 6-dimethylbenzaldoxime by the standard method, 2-hydroxy-4 : 6-dimethylbenzonitrile (1 g.) separated from water in colourless plates, m. p. 178—179°, and on hydrolysis with 90% sulphuric acid at 70° for 4 hours was converted into 2-*hydroxy*-4 : 6-*dimethylbenzamide* which separated from hot water in irregular plates (0·3 g.), m. p. 197° (Found: N, 8·8. $C_9H_{11}O_2N$ requires N, 8·5%). On treatment with 80% sulphuric acid (15 ml.) at 70° for 40 hours this compound (0·5 g.) gave 2-hydroxy-4 : 6-dimethylbenzoic acid which was isolated from the diluted reaction mixture with ether and purified by means of aqueous sodium hydrogen carbonate and then aqueous methanol, forming irregular prisms, m. p. 166° (cf. Stollé and Kuebel, *Ber.*, 1921, **54**, 1213).

(*b*) The potassium derivative (0·5 g.) of the last-mentioned spiran was heated with 2N-sodium hydroxide (10 ml.) on the steam-bath for ½ hour, cooled, and acidified with dilute sulphuric acid. On isolation with ether followed by purification by means of aqueous sodium hydrogen carbonate and then alcohol, 4 : 6-dimethylsalicylic acid (0·13 g.) had m. p. and mixed m. p. 166°.

2-*Hydroxy*-4 : 6-*dimethylpropiophenone*.—Propionic anhydride (500 g.) was added gradually to a well-stirred solution of *m*-xylen-5-ol (460 g.) in water (3 l.) containing sodium hydroxide (160 g.) during 1 hour, and an hour later m-5-*xylyl propionate*, a colourless oil (625 g.), b. p. 167°/56 mm., was isolated (Found: C, 75·0; H, 7·8. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). A mixture of this compound (100 g.) and powdered aluminium chloride (100 g.) was kept at 100° for 5 hours and the complex decomposed in the usual manner. The resulting 2-*hydroxy*-4 : 6-*dimethylpropiophenone* (83 g.) formed long slender needles, m. p. 76°, from dilute alcohol, having a weak purple ferric reaction in alcohol (Found: C, 73·7; H, 7·8. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). The *oxime* separated from dilute methanol in prisms, m. p. 136° (Found: N, 6·9. $C_{11}H_{15}O_2N$ requires N, 7·3%).

3-Ethyl-4 : 6-dimethylcoumarone.—A mixture of 2-hydroxy-4 : 6-dimethylpropiophenone (100 g.), potassium carbonate (85 g.), ethyl bromoacetate (96 g.), and acetone (500 ml.) was heated under reflux for 20 hours. On isolation the resulting *ethyl 3 : 5-dimethyl-2-propionylphenoxyacetate* was obtained as a colourless liquid (146 g.), b. p. 316°/748 mm. (Found: OEt, 17·1. $C_{13}H_{15}O_3{\cdot}OEt$ requires OEt, 17·0%) which by hydrolysis with boiling 10% aqueous-alcoholic sodium hydroxide (400 ml.) for 1 hour gave *3 : 5-dimethyl-2-propionylphenoxyacetic acid*, forming colourless needles (121 g.), m. p. 124°, from benzene (Found: C, 65·8; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

A mixture of this acid (100 g.), sodium acetate (100 g.), and acetic anhydride (300 ml.) was heated (oil-bath) under reflux for 1 hour, cooled, and poured into water. 24 Hours later the resulting colourless liquid *3-ethyl-4 : 6-dimethylcoumarone* (63 g.) was isolated with ether and purified by distillation (b. p. 176°/56 mm.) (Found: C, 83·2; H, 7·6. $C_{12}H_{14}O$ requires C, 82·8; H, 8·1%). A solution of this coumarone (40 g.) in ether (150 ml.) containing hydrogen cyanide (25 ml.) and aluminium chloride (34 g.) was saturated at 0° with hydrogen chloride, kept for 24 hours, and evaporated in a current of air. Hydrolysis of the residue with water (1500 g.) at 0° and then on the steam-bath for 2 hours gave an almost theoretical yield of *3-ethyl-2-formyl-4 : 6-dimethylcoumarone* which was distilled (b. p. 120°/2 mm.) and then crystallised from dilute alcohol, forming colourless plates, m. p. 73° (Found: C, 77·0; H, 6·6. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%), and giving a *2 : 4-dinitrophenylhydrazone* in deep red prisms, m. p. 253°, from benzene–light petroleum (Found: N, 15·0. $C_{19}H_{18}O_5N_4$ requires N, 14·7%).

Oxidation of this aldehyde (1 g.) in acetone (30 ml.) with potassium permanganate (0·6 g.), dissolved in water (20 ml.), yielded *3-ethyl-4 : 6-dimethylcoumarone-2-carboxylic acid* (0·6 g.), forming colourless prisms, m. p. 230°, from acetic acid, identical with the acid (0·7 g.) formed by the cyclisation of ethyl 3 : 5-dimethyl-2-propionylphenoxyacetate (1 g.) with sodium ethoxide (from 0·2 g. of sodium) in alcohol (10 ml.) on the steam-bath for 15 min. (Found: C, 71·8; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

3-Ethyl-4 : 6-dimethylcoumarone-2-acetic Acid.—A mixture of 3-ethyl-2-formyl-4 : 6-dimethylcoumarone (40 g.), hippuric acid (70 g.), sodium acetate (40 g.), and acetic anhydride (250 ml.) was heated on the steam-bath for 2 hours, cooled, and diluted with 50% alcohol (700 ml.). 24 Hours later the *azlactone* was isolated and purified from acetic acid, forming deep yellow needles (61 g.), m. p. 187° (Found: N, 4·3. $C_{22}H_{19}O_3N$ requires N, 4·1%). Hydrolysed by the procedure employed for the azlactone from 2-formyl-3 : 4 : 6-trimethylcoumarone, this compound (30 g.) gave *3-ethyl-4 : 6-dimethyl-2-coumaronepyruvic acid* which separated from dilute alcohol in yellow irregular prisms (17·4 g.), m. p. 203° (Found: C, 69·7; H, 6·0. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). The *oxime* separated from alcohol in fawn-coloured prisms, m. p. 171° (decomp.) (Found: N, 5·2. $C_{15}H_{17}O_4N$ requires N, 5·1%).

Oxidation of the pyruvic acid (17·4 g.) in 5% aqueous potassium hydroxide (100 ml.) with hydrogen peroxide (20 ml. of 100-vol.) at 0° gave *3-ethyl-4 : 6-dimethylcoumarone-2-acetic acid* which crystallised from 50% acetic acid in colourless slender needles (14 g.), m. p. 141° (Found: C, 72·6; H, 6·8. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). Treatment of this acid with excess of boiling thionyl chloride for 30 minutes yielded the chloride which with concentrated ammonia furnished the amide, forming colourless needles, m. p. 172°, from dilute alcohol.

*3-Ethylidene-4′-keto-4 : 6 : 2′-trimethyl*cyclo*pent-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylic Acid* (XV; R = H).—3-Ethyl-4 : 6-dimethylcoumarone-2-acetic acid (10 g.) in chloroform (50 ml.) was converted into the acid chloride with phosphorus pentachloride (10 g.) on the steam-bath for ½ hour. A solution of the resulting crude chloride in ether (150 ml.) was added to a suspension of the ethoxymagnesio-derivative of ethyl acetoacetate (from 6·5 g. of ester, 2·4 g. of alcohol, and 1·15 g. of magnesium) in ether (60 ml.), and the mixture heated under reflux for 6 hours, cooled, and treated with dilute acetic acid. After having been washed with 2N-sodium hydrogen carbonate, 2N-hydrochloric acid, and then water, the ethereal solution was dried and evaporated, leaving a red viscous oil, a solution of which in concentrated sulphuric acid (40 ml.) was kept at −5° for 5 days, poured into ice-water (1 kg.), and extracted with ether (2 × 200 ml.). The combined extracts were washed with water and then 2N-sodium hydrogen carbonate (2 × 25 ml.), dried, and evaporated, leaving a yellow oil which slowly solidified and on crystallisation from light petroleum (b. p. 40—60°) gave *ethyl 3-ethylidene-4′-keto-4 : 6 : 2′-trimethyl*cyclo*penten-2′-ene-1′*-spiro-2-*coumaran-3′-carboxylate* in almost colourless prisms (5—6 g.), m. p. 80°, with a negative ferric and Ehrlich reaction and a positive alkaline nitroprusside reaction (Found: C, 73·6; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). Acidification of the aqueous sodium hydrogen carbonate washings gave only a trace of gum.

A mixture of the red viscous oil (5 g.) and sulphuric acid monohydrate (40 ml.) was heated on the steam-bath for 1 hour, cooled, poured into ice-water (500 ml.), and extracted with ether. The 3-*ethylidene-acid* (XV; R = H) was isolated from the ethereal extracts with 2N-sodium hydrogen carbonate and crystallised from dilute methanol in pale yellow plates (1·1 g.), m. p. 137°, giving the colour reactions of the ethyl ester (Found: C, 72·2; H, 6·1. $C_{18}H_{14}O_4$ requires C, 72·5; H, 6·0%). The same acid was formed by hydrolysis of the aforementioned ethyl ester (1 g.) with 50% alcohol (60 ml.), containing 8% aqueous sodium hydroxide (4 ml.), at 80° for 10 minutes. On isolation it was purified by means of 2N-sodium hydrogen carbonate and then dilute methanol, forming pale yellow plates, m. p. 136°. Esterification of the acid with ethereal diazoethane regenerated the ethyl ester, m. p. and mixed m. p. 80°.

Ozonolysis of the 3-*Ethylidene-ester* (XV; R = Et).—This ester (1 g.), in carbon tetrachloride (30 ml.), was oxidised with ozone according to the method employed for the analogous 3-methylenecoumaran. From the aqueous hydrolysate of the ozonide acetaldehyde was removed by a stream of nitrogen and converted into the dimedone derivative (20 mg.), m. p. 140°, identical with an authentic specimen. The same product (30 mg.), m. p. 140°, was also obtained directly from the filtered hydrolysate in another experiment.

Purified by the procedure employed for the 3-methylenecoumaran product, the gummy solid from the ozonide gave the coumaran-3-one ester (XII; R = Et), m. p. and mixed m. p. 91—92°.

Similarly, ozonolysis of the 3-ethylidene acid gave acetaldehyde and the coumaran-3-one acid (XII; R = H), m. p. and mixed m. p. 158—159°.

4 : 6-*Dimethylcoumarone*-2-*carboxylic Acid* (XVIII; R = OH).—2-Hydroxy-4 : 6-dimethylbenzaldehyde (Duff, *J.*, 1941, 547) gave a 2 : 4-*dinitrophenylhydrazone* in squat red needles, m. p. 253°, from light petroleum (b. p. 60—80°) (Found: N, 17·3. $C_{15}H_{14}O_5N_4$ requires N, 17·0%). Interaction of the aldehyde (4·9 g.) with methyl bromoacetate (51 g.) and potassium carbonate (48 g.) in boiling acetone (300 ml.) for 8 hours gave *methyl* 2-*formyl*-3 : 5-*dimethylphenoxyacetate* which formed colourless needles, m. p. 98°, from dilute methanol (Found: C, 64·7; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%) and gave a 2 : 4-*dinitrophenylhydrazone* in slender orange needles, m. p. 188°, from dilute alcohol (Found: N, 14·0. $C_{18}H_{18}O_7N_4$ requires N, 13·9%). This ester exhibits phototropy, becoming yellow on exposure to light and then reverting to the colourless form in the dark. On hydrolysis with 2N-aqueous-methanolic sodium hydroxide it gave 2-formyl-3 : 5-dimethylphenoxyacetic acid which separated from dilute acetic acid in needles, m. p. 170°, and yielded a 2 : 4-*dinitrophenylhydrazone* in orange needles, m. p. 192°, from dilute alcohol (Found: N, 14·5. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

A solution of methyl 2-formyl-3 : 5-dimethylphenoxyacetate (5 g.) in methanol (50 ml.), containing sodium methoxide (from 1·1 g. of sodium), was heated on the steam-bath for 15 minutes, diluted with water (50 ml.), and again heated for 15 minutes. The cooled reaction mixture was extracted with ether to remove a little 4 : 6-dimethylcoumarone (0·2 g.), b. p. 219°/760 mm. (picrate, m. p. 61°) (Stoermer, *Annalen*, 1900, **312**, 295) and then acidified, giving a mixture of 4 : 6-*dimethylcoumarone*-2-*carboxylic acid* and 2-formyl-3 : 5-dimethylphenoxyacetic acid. On being cooled a solution of this mixture in hot acetic acid deposited the former acid in irregular prisms (2·4 g.), m. p. 257°, after recrystallisation from dilute alcohol, with a blue sulphuric acid reaction (Found: C, 69·5; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%). Prepared with thionyl chloride, the chloride from this acid gave the *amide* which formed plates, m. p. 173°, from dilute alcohol (Found: N, 7·4. $C_{11}H_{11}O_2N$ requires N, 7·4%).

On dilution with water the acetic acid liquor left on the removal of 4 : 6-dimethylcoumarone-2-carboxylic acid gave 2-formyl-3 : 5-dimethylphenoxyacetic acid (1 g.), m. p. and mixed m. p. 170°, after recrystallisation from dilute alcohol.

4 : 6-*Dimethylcoumarone*-2-*acetic Acid* (XIX; R = OH).—Formed when 4 : 6-dimethylcoumarone-2-carboxylic acid (1 g.) was heated with thionyl chloride (2 ml.) under reflux for 45 min., the acid chloride was purified by distillation and obtained as colourless crystals (0·9 g.), b. p. 140°/2 mm., m. p. 75°. A solution of this product in ether (20 ml.) was added to a three-fold excess of ethereal diazomethane at 0° and 24 hours later the diazo-ketone (XVIII; R = CHN_2) (0·4 g.) was collected, forming long yellow needles, m. p. 147°, from methanol; a further quantity (0·5 g.) was obtained on evaporation of the ethereal liquor. When this compound was subjected to the Wolff rearrangement with methanol and silver oxide under the usual conditions the yields of the requisite acetic acid were indifferent (50 mg. of crude product from 1 g. of diazo-ketone) and the modified procedure of Wilds and Meader (*J. Org. Chem.*, 1948, **13**, 763) was adopted. A flask containing a mixture of the diazo-ketone (1 g.), benzyl alcohol (5 ml.), and dimethylaniline (5 ml.) was immersed in an oil-bath at 190° and the reaction,

which commenced after 3 minutes, was complete in about 15—20 min. After having been washed with 2N-hydrochloric acid an ethereal solution (100 ml.) of the reaction mixture was evaporated and the residual red oil heated with 40% aqueous potassium hydroxide (5 ml.) on the steam-bath for 2 hours, diluted with water (20 ml.), extracted with ether, treated with charcoal, filtered, and acidified, giving a mixture of 4 : 6-*dimethylcoumarone-2-acetic acid* (XIX; R = OH) (0·3 g.) and 4 : 6-dimethylcoumarone-2-carboxylic acid (0·1 g.) which were separated by fractional crystallisation from dilute methanol. The more soluble 4 : 6-dimethylcoumarone-2-acetic acid formed colourless needles, m. p. 113°, having a violet sulphuric acid reaction (Found: C, 70·2; H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

Prepared from 4 : 6-dimethylcoumarone-2-acetic acid (1·6 g.) with phosphorus pentachloride (1·6 g.) in chloroform (50 ml.) at room temperature for ½ hour and then at 40° for 15 minutes, the acid chloride was dissolved in ether (50 ml.) mixed with ethereal ethoxymagnesio-derivative of ethyl acetoacetate (from 1·3 g. of ester), refluxed for 6 hours, and treated with a little dilute hydrochloric acid. On isolation with ether the crude product was dissolved in cooled concentrated sulphuric acid and, after being kept at −5° for 3 days, the solution was poured on ice and extracted with ether. The combined extracts were washed with alkali, dried, and evaporated, leaving a neutral *substance* which separated from light petroleum (b. p. 60—80°) in pale yellow needles (0·15 g.), m. p. 156° (Found: C, 68·1; H, 6·2. $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·3%). This product, which gave a negative Ehrlich reaction and a positive alkaline nitroprusside reaction, had an ultra-violet absorption spectrum totally different from that of usnolic acid and its analogues.

Resolution of Optically Inactive Usnic Acid.—(+)-Usnic acid, m. p. 204°, $[\alpha]_D^{20}$ +495° (*c*, 0·5 in $CHCl_3$) was isolated from *Usnea florida* (Web), *U. florida* (Ach), and *Usnea hirta* (Ach) which had been collected in Wales. (+)-Usnic acid (0·5 g.), dissolved in 8% aqueous sodium hydroxide (20 ml.), was treated with methyl sulphate (1·5 c.c.), added in 3 portions, the solution was acidified, and the precipitate was well washed with water and heated with 75% methanol (20 ml.). On cooling, the filtered solution deposited (+)-O-*methylusnic acid* which crystallised from acetone in bright yellow prisms (0·25 g.), m. p. 136°, $[\alpha]_D^{20}$ +355° (*c*, 2·0 in $CHCl_3$) (Found: C, 63·1; H, 5·0; OMe, 8·6. $C_{18}H_{15}O_6$·OMe requires C, 63·7; H, 5·0; OMe, 9·0%).

A solution of (±)-usnic acid (2 g.) (Schöpf and Heuck, *Annalen*, 1927, **459**, 233) in the minimum amount of acetone was treated with (−)-brucine (2·35 g.), dissolved in methanol (10 ml.), and the greater part of the acetone evaporated on the steam-bath. On cooling, the mixture deposited (−)-brucine (±)-usnate in small colourless plates, m. p. 213° (decomp.) $[\alpha]_D^{20}$ −10° (*c*, 5·0 in $CHCl_3$). This salt (4 g.) was boiled with methanol (100 ml.) for 2 minutes and filtered, giving solid (A) and solution (B). Solid (A) was then extracted with boiling methanol (100 ml.) for 5 min., yielding solid (A_1) and solution (B_1). Repetition of this process with (A_1) and methanol (50 ml.) gave solid (A_2) and solution (B_2). The solutions (B), (B_1), and (B_2) were combined and diluted with water (1 l.), and 24 hours later the solid (C) was collected, leaving the filtrate (D).

The almost colourless residue (A_2) had m. p. 226° (decomp.), $[\alpha]_D^{20}$ +212° (*c*, 2·5 in $CHCl_3$) and was indistinguishable from a specimen of the (−)-brucine salt of authentic (+)-usnic acid which had m. p. 227° (decomp.), $[\alpha]_D^{20}$ +222° (*c*, 5·0 in $CHCl_3$). Decomposition of this salt (A_2) with 2N-sodium hydroxide followed by acidification with 2N-hydrochloric acid gave (+)-usnic acid which was purified from chloroform and alcohol, forming long yellow prisms, m. p. 204°, $[\alpha]_D^{20}$ +467° (*c*, 5·0 in $CHCl_3$), identical with a natural specimen.

Treatment of the filtrate (D) with 2N-hydrochloric acid gave (−)-usnic acid which on purification from chloroform and alcohol had m. p. 203°, $[\alpha]_D^{20}$ −367° (*c*, 5·0 in $CHCl_3$), identical with an authentic specimen. The (−)-brucine salt was prepared from this (−)-acid and had m. p. 222° (decomp.), $[\alpha]_D^{20}$ −240° (*c*, 0·3 g. in $CHCl_3$), whilst the (−)-brucine salt of authentic (−)-usnic acid had m. p. 224° (decomp.), $[\alpha]_D^{20}$ −254° (*c*, 5·0 in $CHCl_3$).

Usnolic Acid.—The following improved method was employed for the preparation of this compound from usnic acid. A solution of usnic acid (1 g.) in sulphuric acid monohydrate (10 ml.) was kept at 40—50° for 1 hour, cooled, and poured on ice (100 g.). The reaction vessel was washed with water (20 ml.) and then ethanol (20 ml.), and the washings were added to the main product. This mixture was heated to about 95—98°, whereupon the original flocculent precipitate of usnolic acid became macrocrystalline. On isolation this product (0·85—0·9 g.) formed yellow plates, m. p. 230—231° (decomp.) (cf. Stenhouse and Groves, *J.*, 1881, **39**, 234, and Curd and Robertson, Part V, *J.*, 1937, 894). Methylation of usnolic acid (1 g.) with methyl sulphate (1·25 g.) and potassium carbonate (1·25 g.) in boiling acetone (50 ml.) for 5 hours gave *methyl* O-*methylusnolate* (IV; R = Me, R′ = CO_2Me) which separated from light petroleum (b. p.

40—60°) and then dilute acetic acid in pale yellow rectangular plates (0·5 g.), m. p. 134° [Found: C, 63·8; H, 5·6; OMe, 17·8. $C_{13}H_{14}O_5(OMe)_2$ requires C, 64·5; H, 5·4; OMe, 16·7%]. This compound gives an emerald-green ferric, a blue Ehrlich, and a violet alkaline nitroprusside reaction. Treatment of usnolic acid in 1 : 1 (vol.) ether–chloroform with ethereal diazomethane for 20 min., followed by decomposition of the excess of diazomethane with acetic and evaporation of the solution, left a residue which crystallised in contact with methanol, giving an almost theoretical yield of methyl *O*-methylusnolate, m. p. and mixed m. p. 134°. Reaction with diazomethane for shorter periods, *e.g.*, 10 min., gave a mixture of methyl usnolate, m. p. 202°, along with a little methyl *O*-methylusnolate (Widmann, *Annalen*, 1902, **324**, 139) whilst prolonged treatment gave a gummy product.

Hydrogenation of usnolic acid (1 g.) in ethyl acetate (250 ml.) with hydrogen (2 mols. absorbed) with a platinum catalyst (0·1 g.) furnished a yellow gummy product which, on purification with aqueous sodium hydrogen carbonate to remove resin and then by crystallisation from dilute methanol, gave *tetrahydrousnolic acid* in pale yellow needles (0·65 g.), m. p. 134° (decomp.) (Found: C, 59·3; H, 5·8. $C_{18}H_{22}O_8$ requires C, 59·0; H, 6·0%).

Ozonolysis of methyl *O*-methylusnolate (0·5 g.) in ethyl acetate (60 ml.), followed by treatment of the product with water for 24 hours, gave an aqueous solution containing formaldehyde which was isolated as the dimedone derivative, m. p. and mixed m. p. 191°, together with a gummy solid. Crystallised from methanol and then benzene–light petroleum (b. p. 60—80°), this gave the *methyl ether* of methyl 7-acetyl-4 : 6-dihydroxy-3 : 4′-diketo-5 : 2′-dimethyl*cyclo*pent-2′-ene-1′-*spiro*-2-coumaran-3′-carboxylate (V; R = Me, R′ = CO_2Me) in colourless prisms (0·2 g.), m. p. 137—139°, which reduced Fehling's solution and gave a red ferric and a transient blue alkaline nitroprusside reaction [Found: C, 61·1; H, 4·9; OMe, 15·2. $C_{17}H_{12}O_6(OMe)_2$ requires C, 61·0; H, 4·9; OMe, 16·6%]. Oximation of (V; R = Me, R′ = CO_2Me) by the sodium acetate method for 2 days at room temperature gave a dioxime, which formed pointed plates, m. p. 243° (decomp.), with a reddish-purple ferric reaction and contained methanol of crystallisation [Found: N, 6·2; OMe, 22·9. $C_{17}H_{14}O_6N_2(OMe)_2$,MeOH requires N, 6·4; OMe, 21·3%].

Attempted Resolution of Usnolic Acid.—A solution of the acid (2 g.) in the minimum amount of hot acetone was mixed with (−)-brucine (2·3 g.), dissolved in acetone (20 ml.), and the mixture concentrated; the *brucine* salt of usnolic acid separated in irregular fawn-coloured prisms (4·2 g.), m. p. 190°, $[\alpha]_D^{20}$ −10° (*c*, 4·0 in $CHCl_3$) (Found: N, 4·1. $C_{41}H_{42}O_{11}N_2$ requires N, 3·8%). This salt (4 g.) was digested with hot methanol (50 ml.) for 2 min. and the insoluble residue then repeatedly extracted with boiling methanol (100 ml.) until the weight was reduced to about 1·5 g. This residual solid (0·5 g.), m. p. 209° (decomp.), $[\alpha]_D^{20}$ −30° (*c*, 2·0 in $CHCl_3$), was decomposed with 2N-hydrochloric acid (2 ml.) in methanol (10 ml.), and the precipitated usnolic acid twice recrystallised from dilute methanol containing a drop of dilute hydrochloric acid, forming plates (0·2 g.), m. p. 233°, $[\alpha]_D^{20}$ −19° (*c*, 1·0 in MeOH). Treatment of this product (0·25 g.) with sulphuric acid monohydrate (5 ml.) at 50° for 1 hour gave usnolic acid, m. p. 233°, after purification which had a zero rotation and gave a brucine salt, m. p. 190°, $[\alpha]_D^{20}$ −10° (*c*, 0·25 in $CHCl_3$).

On dilution with water followed by acidification with 2N-hydrochloric acid the initial extract (50 ml.) of the brucine salt gave usnolic acid, m. p. 233°, $[\alpha]_D^{20}$ +31° (*c*, 1·0 in MeOH), after being twice recrystallised from dilute methanol. The brucine salt of this product had m. p. 203° $[\alpha]_D^{20}$ −3·3° (*c*, 0·3 in $CHCl_3$).

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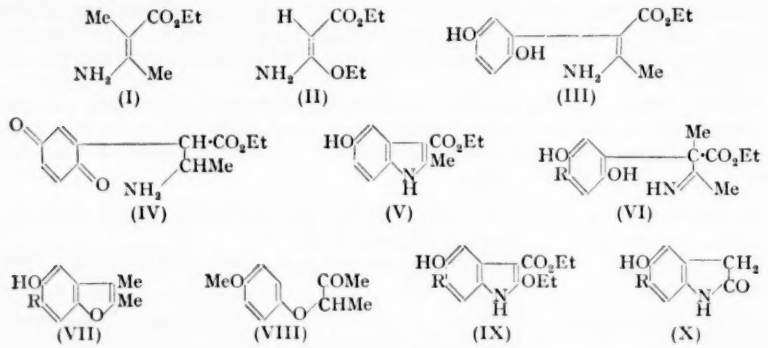
251. *Some Extensions of the Synthesis of Hydroxyindoles from* p-*Benzoquinones.*

By R. J. S. Beer, H. F. Davenport, and Alexander Robertson.

Ethyl β-amino-α-methylcrotonate reacts with *p*-benzoquinone and methoxy-*p*-benzoquinone to give the quinol derivatives (VI; R = H and OMe) which, with hot alkali, are converted into 5-hydroxy- (VII; R = H) and 5-hydroxy-6-methoxy-2 : 3-dimethylcoumarone (VII; R = OMe) respectively. With ethyl β-amino-β-ethoxyacrylate, ethyl 2-ethoxy-5-hydroxy- and ethyl 2-ethoxy-5-hydroxy-6-methoxy-indole-3-carboxylate are formed and respectively give the corresponding 5-hydroxy- and 5-hydroxy-6-methoxy-oxindole on hydrolysis.

Condensation of ethyl β-aminocrotonate with *p*-benzoquinones provided a route to certain 5-hydroxyindole derivatives (Beer, Clarke, Davenport, and Robertson, *J.*, 1951, 2029; cf. Nenitzescu, *Bull. Soc. Chim. Roumania*, 1929, **11**, 37) and the present paper describes extensions of the reaction with esters formally similar to ethyl β-aminocrotonate, *e.g.*, (I) and (II). Indole formation by this method probably proceeds by way of intermediates of type (III) which cyclise by loss of water to esters of 5-hydroxyindole-3-carboxylic acids of type (V). Harley-Mason (personal communication) has suggested that intermediates of the type (IV) are also possible. Either mechanism is consistent with the fact that the final products in the cases examined are 5-hydroxy- and not 6-hydroxy-indoles which would obtain if the initial reaction involved the attachment of the amino-group to the quinone nucleus.

The interaction of ethyl β-amino-α-methylcrotonate (I) with *p*-benzoquinone gave a somewhat unstable phenolic base, having the composition of a hydrate of the quinol (VI; R = H), which might conceivably have cyclised to form an indolenine. This did not occur, but on treatment with hot aqueous sodium hydroxide the quinol hydrate furnished 5-hydroxy-2 : 3-dimethylcoumarone (VII; R = H) with the liberation of ammonia. The structure of (VII; R = H) was substantiated by an unambiguous synthesis. 3-*p*-Methoxyphenoxybutan-2-one (VIII) was formed by the alkylation of quinol monomethyl ether with 3-chlorobutan-2-one and cyclised with sulphuric acid to give a good yield of 5-methoxy-2 : 3-dimethylcoumarone which, on demethylation, yielded 5-hydroxy-2 : 3-dimethylcoumarone (VII; R = H).



The quinol (VI; R = OMe), similarly formed from methoxy-*p*-quinone, was more stable but on treatment with hot alkali also furnished a coumarone which, by analogy, is 5-hydroxy-6-methoxy-2 : 3-dimethylcoumarone (VII; R = OMe).

The condensation of ethyl β-amino-β-ethoxyacrylate (II) with *p*-benzoquinone gave the expected ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate (IX; R = H) which, however, was surprisingly resistant to mild alkaline hydrolysis and, with hot concentrated alkali under more drastic conditions, decomposed to intractable products. By means of boiling

dilute hydrochloric acid, the compound was smoothly converted into 5-hydroxyoxindole (X; R = H) which was also obtained in poor yield when *N*-chloroacetyl-*p*-anisidine was heated with aluminium chloride according to Stolle's procedure (cf. Porter, Robinson, and Wyler, *J.*, 1941, 620).

The compound obtained in this reaction by Giovanni and Portmann (*Helv. Chim. Acta*, 1948, **31**, 1381) and regarded by them as 5-methoxyoxindole is clearly 5-hydroxyoxindole, as suggested by Julian ("Heterocyclic Compounds," John Wiley and Sons, New York, Vol. III, 1952, p. 145). Methylation of the 2-ethoxy-5-hydroxyindole ester (IX; R = H) with methyl sulphate and alkali gave a product which is apparently ethyl 2-ethoxy-5-methoxy-1-methylindole-3-carboxylate, since on treatment with hot dilute hydrochloric acid it furnished 5-methoxy-1-methyloxindole.

When *p*-benzoquinone was replaced by methoxy-*p*-benzoquinone in the initial condensation the resulting ethyl 2-ethoxy-5-hydroxy-6-methoxyindole-3-carboxylate (IX; R = OMe) had properties similar to those of (IX; R = H), and on hydrolytic decomposition with warm acid gave 5-hydroxy-6-methoxyoxindole (X; R = OMe).

Although *N*-alkyl and *N*-aryl derivatives of ethyl β-aminocrotonate condense with *p*-benzoquinone to give hydroxyindoles, the *N*-acetyl derivative of the ester, as was expected, failed to react. A similar lack of reactivity was shown by ethyl aminomethylenemalonate.

Experimental

5-Hydroxy-2 : 3-dimethylbenzofuran.—(*a*) Interaction of ethyl β-amino-α-methylcrotonate (Conrad and Epstein, *Ber.*, 1887, **20**, 3055) (5·6 g.) and *p*-benzoquinone (4·0 g.) in boiling acetone (30 ml.) for 1 hour gave ethyl α-(2 : 5-dihydroxyphenyl)-β-imino-α-methylbutyrate which separated from ethyl acetate–light petroleum (b. p. 40—60°) as a *hydrate* in colourless prisms (3·0 g.), m. p. 89—90° (Found: C, 58·0; H, 7·3; N, 5·3. $C_{13}H_{17}O_4N,H_2O$ requires C, 58·0; H, 7·1; N, 5·2%). With boiling 2N-sodium hydroxide (20 ml.) in nitrogen this compound (0·5 g.) gave ammonia and *5-hydroxy-2 : 3-dimethylcoumarone*. This product was isolated with ether and purified by distillation at 90°/0·1 mm., followed by crystallisation from light petroleum (b. p. 80—100°), forming rosettes of colourless needles (0·2 g.), m. p. 79° (Found: C, 74·3; H, 6·1. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

(*b*) Alkylation of quinol monomethyl ether (5·0 g.) with 3-chlorobutan-2-one (3·0 g.) and potassium carbonate (10 g.) in boiling acetone (20 ml.) for 2 hours furnished 3-*p*-methoxyphenoxybutan-2-one as a colourless oil (4·0 g.), b. p. 164—169°/30 mm., characterised as the *semicarbazone*, needles, m. p. 114° (from methanol) (Found: N, 16·6. $C_{12}H_{17}O_3N_3$ requires N, 16·7%). Cyclisation of this ketone (4 g.) was effected with concentrated sulphuric acid (10 ml.) at 0° for 10 minutes and the resulting 5-methoxy-2 : 3-dimethylbenzofuran (2 g., b. p. 140/20 mm.) was isolated with ether after addition of ice-water and basification with aqueous sodium hydroxide. A mixture of this product (1 g.), hydriodic acid (8 ml.; *d* 1·7), and acetic acid (5 ml.) was gently heated under reflux for 30 minutes, cooled, diluted with water (100 ml.), treated with a little sulphur dioxide to remove traces of iodine, neutralised with sodium hydrogen carbonate, and extracted with ether. Distillation of the residue left on evaporation of the extracts gave 5-hydroxy-2 : 3-dimethylbenzofuran (0·3 g.), b. p. 90°/0·1 mm., m. p. 79°, after purification from light petroleum (b. p. 80—100°), identical with a specimen prepared by route (*a*).

5-Hydroxy-6-methoxy-2 : 3-dimethylbenzofuran.—Formed by condensation of ethyl β-amino-α-methylcrotonate (5·2 g.) and methoxy-*p*-benzoquinone (5 g.) in boiling acetone during 1 hour, *α-(2 : 5-dihydroxy-4-methoxyphenyl)-β-imino-α-methylbutyrate* crystallised from 95% alcohol in colourless prisms (7·4 g.), m. p. 154° (Found: C, 59·5; H, 6·7; N, 5·0. $C_{14}H_{19}O_5N$ requires C, 59·8; H, 6·8; N, 5·0%). On being heated under reflux with 2N-sodium hydroxide (30 ml.) in nitrogen for 1 hour, this product gave *5-hydroxy-6-methoxy-2 : 3-dimethylbenzofuran* which was purified by distillation at 90°/0·01 mm. and then by crystallisation from light petroleum (b. p. 80—100°), forming colourless needles (0·45 g.), m. p. 112° (Found: C, 68·6; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%).

5-Hydroxyoxindole.—(*a*) A solution of ethyl β-amino-β-ethoxyacrylate (Glickman and Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017) (3 g.) in alcohol (5 ml.) was added to *p*-benzoquinone (5 g.) in hot alcohol (15 ml.) and, after the initial vigorous reaction had subsided, the mixture was heated on the steam-bath for 1 hour. Kept at 0° this reaction mixture deposited *ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate*, forming colourless plates (3 g.), m. p. 168° (from

alcohol), which reduced Tollens' reagent but had a negative Ehrlich reaction [Found, in a specimen dried in a vacuum at 80°: C, 62·5; H, 6·1; N, 5·9; OEt, 36·0. $C_9H_5O_2N(OEt)_2$ requires C, 62·6; H, 6·0; N, 5·6; OEt, 36·1%]. This compound was resistant to alkaline hydrolysis and after being boiled with 2N-sodium hydroxide for 2 hours was largely unchanged. When heated with 2N-hydrochloric acid (30 ml.) the ester (1 g.) slowly dissolved and distillation of the solution in a vacuum left a residue of *5-hydroxyoxindole* which was purified by sublimation at 160°/0·1 mm. and then by crystallisation from ethyl acetate–light petroleum (b. p. 40—60°), forming colourless needles (0·7 g.), m. p. about 270°, with some previous decomposition (Found: C, 64·4; H, 4·6; N, 9·1. $C_8H_7O_2N$ requires C, 64·4; H, 4·7; N, 9·4%).

(*b*) An intimate mixture of *N*-chloroacetyl-*p*-anisidine (3·1 g.) and powdered aluminium chloride (4·4 g.) was kept at 120° for 10 minutes, then heated to 240° in the course of 40 minutes, cooled, and decomposed with ice and hydrochloric acid in the usual manner. The resulting solution was heated on the steam-bath for 10 minutes, filtered to remove tarry impurities, cooled, and extracted with ethyl acetate, giving, after purification, 5-hydroxyoxindole, m. p. 265° (decomp.) undepressed on addition of a specimen obtained by method (*a*). The product described by Giovanni and Portmann (*loc. cit.*) as 5-methoxyoxindole was stated to form needles, decomp. 270°.

In an attempted cyclisation experiment at 190° the product was mainly *p-chloroacetamidophenol*, forming colourless needles, m. p. 146°, from water (Found: N, 7·8. $C_8H_8O_2NCl$ requires N, 7·5%).

5-Methoxy-1-methyloxindole.—Methylation of ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate (3·0 g.) with methyl sulphate and warm alkali gave the *dimethyl* derivative (2·0 g.) which formed almost colourless needles, m. p. 95—96°, from ethanol (Found: C, 65·2; H, 6·9; N, 5·1. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9; N, 5·05%). This product (0·5 g.) slowly dissolved in boiling 2N-hydrochloric acid to a colourless solution, which, on evaporation, furnished 5-methoxy-1-methyloxindole, forming colourless blades (0·25 g.), m. p. 97° (depressed by admixture with the starting material) from light petroleum (b. p. 80—100°) (Found: C, 67·7; H, 6·0; N, 7·65; OMe, 17·1. Calc. for $C_9H_8ON{\cdot}OMe$: C, 67·8; H, 6·2; N, 7·9; OMe, 17·5%) (Porter, Robinson, and Wyler, *loc. cit.*, give m. p. 92°).

5-Hydroxy-6-methoxyoxindole.—Condensation of methoxy-*p*-benzoquinone (2·6 g.) and ethyl β-amino-β-ethoxyacrylate (3·0 g.) in hot alcohol gave *ethyl 2-ethoxy-5-hydroxy-6-methoxyindole-3-carboxylate* which separated from alcohol in colourless plates (2·6 g.), m. p. 160° (Found: C, 60·6; H, 6·2; N, 4·9. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%). Treatment of this ester (1·0 g.) with hot 2N-hydrochloric acid (30 ml.) for 30 minutes gave *5-hydroxy-6-methoxyoxindole* which was purified by sublimation at 140°/0·01 mm. and then by crystallisation from alcohol, forming colourless needles (0·65 g.), m. p. 273° (decomp.) (Found: C, 59·9; H, 4·7; N, 7·9. $C_9H_9O_3N$ requires C, 60·3; H, 5·0; N, 7·8%).

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252. *Some Physical Investigations of the Behaviour of Bacterial Surfaces. Part II.* The Variation of the Electrophoretic Mobility of* Aerobacter aerogenes *with the Age of the Culture and the Nature of the Culture Medium.*

By P. J. BARRY and A. M. JAMES.

No change in the electrophoretic mobility of *Aerobacter aerogenes* has been detected during growth in a range of completely synthetic media, despite marked differences in cell metabolism. Growth in more complex media, such as meat broth and agar, produces no change in the cell surface as revealed by the constancy of the mobility.

PREVIOUS investigations (Part I *) indicated little difference in the nature of the surface of young and old cells. A more detailed study of the electrophoretic mobility during the growth of *Aerobacter aerogenes* under a wide range of conditions is now reported.

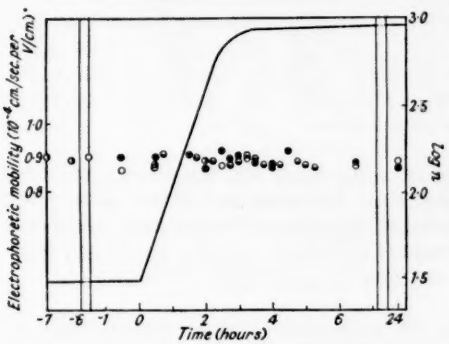
Moyer (*J. Bact.*, 1936, **32**, 433) and Shibley (*J. Exp. Med.*, 1924, **40**, 453) working with different strains of bacteria have found that in all cases young cells have a lower mobility

* Part I, *J.*, 1952, 3340.

than older ones, whilst, on the other hand, Pedlow and Lisse (*J. Bact.*, 1936, **31**, 235) and Buggs and Green (*ibid.*, 1935, **30**, 453) have shown that *Escherichia coli* grown either in peptone or on agar has a constant mobility for up to 10 days' incubation. The variation of the mobility of the *typhoid bacillus* with age is dependent on the growth medium, some media causing a decrease, others an increase (Watrous, *J. Infect. Dis.*, 1937, **60**, 47). Selective removal of lipid and amphoteric materials from the bacterial cell surface has led Dyar (*J. Bact.*, 1948, **56**, 821) to conclude that the surface composition depends on the growth medium.

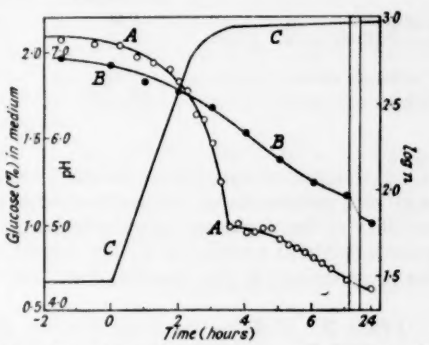
In all these previous experiments, however, growth has occurred in complex media, and the change from one medium to another is made without detailed knowledge of the changes in chemical environment concerned. We have overcome this by using simple synthetic media, their chemical composition being subjected to rigid control. In addition to the electrophoretic mobility a study was made of the differences in the rates of growth, and of hydrogen-ion production and glucose utilisation during growth in these different media, in an attempt to correlate surface changes with changes in certain metabolic functions.

FIG. 1. *Variation of electrophoretic mobility of* Aerobacter aerogenes *during growth in glucose–ammonium sulphate medium.*



(The differently shaded circles represent different experiments; the solid line is the average growth curve.)

FIG. 2. *Variation of* pH *and glucose content of the medium during the growth of* Aerobacter aerogenes.



(*A*, pH *values.* B, *Glucose concentration.* C, *Growth curve.*)

Variation of the Electrophoretic Mobility.—(*a*) *Growth in glucose–ammonium sulphate medium.* The relation between the electrophoretic mobility and age for cells grown in the normal medium is shown in Fig. 1. This includes observations made in several independent experiments, and since the length of the lag phase was variable, the graph has been plotted so that the end of the lag phase is zero; *i.e.* observations appearing in the lag are at negative time. The mobility remains constant, within the limits of experimental error, during the

TABLE 1. *Growth in media containing different amino-acids.*

	Electrophoretic mobility ($cm.^2\ sec.^{-1}\ v^{-1} \times 10^4$)					
	Glycine	Alanine	Serine	Aspartic acid	Glutamic acid	Tyrosine
Lag phase	0·91	0·91	0·91	0·87	0·88	0·88
Logarithmic growth phase	0·92	0·90	0·89	0·88	0·90	0·90
	(3) *	(4)	(7)	(6)	(6)	(5)
Stationary phase	0·87	0·87	0·87	0·87	0·88	0·87
M.g.t.	120′	48′	60′	108′	84′	108′

* Figures in parentheses show the number of observations made in the growth phase.

complete growth cycle, the average being $0{\cdot}89 \times 10^{-4}$ cm.^{2} sec.$^{-1}$ volt^{-1}, towards the positive electrode. This result is further supported by our previous observation that the behaviour of old and young cells towards change of ionic strength and pH was sensibly the same.

(*b*) *Growth in glucose amino-acid media.* The following amino-acids were used to give a

representative selection : glycine, alanine, serine, aspartic acid, glutamic acid, and tyrosine. The mobility was constant throughout the growth cycle and numerically the same as in the previous series (Table 1).

(*c*) *Growth in ammonium sulphate media containing various sources of carbon.* In the normal medium a monosaccharide was used, and we considered any possible variations which might accompany growth in a medium containing a disaccharide (sucrose), a polysaccharide (starch), or a simple carbon source (glycerol). In all these experiments, cells adapted for growth in the different media were used and, in addition, cells trained and grown in glucose were used to inoculate a glycerol medium. In the last case the growth curve revealed that initially the organisms grew on the glucose carried over in the inoculum, and later, when this was exhausted, there was an arrest in the growth accompanying the utilisation of a different carbon source. Again the mobility was constant throughout the growth cycle and not significantly different from that recorded in Fig. 1 (Table 2).

TABLE 2. *Growth in media containing different carbon sources.*

	Electrophoretic mobility (cm.^{2} sec.$^{-1}$ v^{-1} × 10^4)				
	Glycerol (untrained)	Glycerol (trained)	Glucose	Sucrose	Starch
Lag phase	0·90	0·89	0·90	0·88	0·89
Logarithmic growth phase	0·90	0·88	0·88	0·90	0·89
	(4)	(5)	(6)	(5)	(4)
Stationary phase	0·90	0·87	0·90	0·87	0·89
M.g.t.	* 42′, 100′	55′	33′	45′	53′

* Composite growth curve.

(*d*) *Complex media.* In an attempt to repeat earlier work, we considered a wider range of growth conditions by the use of a richer medium. The constancy of the electrophoretic mobility of the organism, already demonstrated with amino-acids, was maintained during growth (without aeration at 37°) in a meat broth (Lab-Lemco, Oxoid preparation) both in the presence and in the absence of glucose, and also, on agar slopes (Table 3).

TABLE 3. *Mobility* (cm.^{2} sec.$^{-1}$ v^{-1} × 10^4) *of* Aerobacter aerogenes *during growth in Lab-Lemco medium, in the presence and absence of glucose, and on agar slopes.*

Time (days)	7 hr.	1	2	4	5	7	9	11
Lab-Lemco (+ glucose)	—	0·87	0·90	0·84	—	0·86	—	0·89
Lab-Lemco (− glucose)	—	0·89	0·92	0·88	—	0·89	—	0·92
Agar	0·90	0·91	0·83	—	0·91	—	0·86	—

Variation of Metabolism during Growth in Various Media.—Variations of certain metabolic functions during growth in different media are apparent from the different rates of growth, hydrogen-ion production, and glucose utilisation, and also from previous work on the different enzyme systems in the cell (dehydrogenase, James and Hinshelwood, *Trans. Faraday Soc.*, 1948, **44**, 967; catalase, Cole and Hinshelwood, *ibid.*, 1947, **43**, 266). The pH values and the glucose concentrations [estimated by a modification of the Shaffer–Hartmann method (*J. Biol. Chem.*, 1920, **45**, 365)] at different times during the growth of the organism in the normal medium are plotted in Fig. 2. Similar determinations were made during growth in the other culture media. However, despite differences in the metabolism revealed by these observations the mobility remained constant.

EXPERIMENTAL

The culture of *Aerobacter aerogenes* was grown in a standard culture medium which consisted of glucose (19·2 g./l.), potassium dihydrogen phosphate (3·46 g./l.), ammonium sulphate (0·96 g./l.) and magnesium sulphate (0·04 g./l.) adjusted to pH 7·12 with 4N-sodium hydroxide.

Variation of the Nitrogen and Carbon Sources.—In one series of experiments the ammonium sulphate was replaced by amino-acids in concentrations giving an equivalent supply of nitrogen. In the other series the glucose was replaced by glycerol (7·7 g./l.), sucrose (9·6 g./l.), or starch

(0·75 g./l.). In all cases the growth rate was determined turbidometrically as previously described.

The cells were adapted for growth in each medium by at least 10 previous sub-cultures. 25 Ml. of a 24-hour old culture, suitably trained, were used as the inoculum for a litre of fresh medium. This was aerated at 40° and samples were withdrawn at convenient intervals for the determination of electrophoretic mobility (Part I), pH value, glucose concentration, and bacterial count. Samples withdrawn for mobility determination were centrifuged, washed twice with 0·0067M-phosphate buffer solution at pH 7·03, and finally re-suspended in that menstruum.

Discussion

It has been shown that the electrophoretic mobility of *Aerobacter aerogenes* determined under the given conditions is constant and independent of both the age of the culture and the nature of the culture medium. The individual observations are identical within the specified limits of experimental error and in no case has an observation varied from the mean by an amount comparable with that reported by other workers using different organisms (Moyer and Watrous, *locc. cit.*).

Growth is accompanied by the production of acid (cf. the rapid fall in pH shown in Fig. 2). Such variations would undoubtedly give rise to a change in the ζ-potential (Fig. 4, Part I), but that growth in wide ranges of hydrogen-ion concentration is not accompanied by irreversible changes in the nature of the surface responsible for electrokinetic phenomena is shown by the constancy of the mobility after the organisms had been washed in the phosphate buffer solution. Similarly, both growth intermediates and toxins will be present in the medium during growth, but these also fail to give rise to irreversible changes in the nature of the surface.

Whereas the electrophoretic mobility of the organisms constitutes a satisfactory standard of reference for future work, we have, however, concluded that, at least with reference to *Aerobacter aerogenes*, electrophoretic determinations are unlikely to throw further light on the problems of the bacterial cell surface during growth.

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253. *Hydroperoxides as Initiators for the Polymerisation of Styrene.*

By W. Cooper.

A number of hydroperoxides have been examined as initiators for the polymerisation of styrene. Apart from more rapid initiation due to aryl groups, changes of structure have only slight effect. The proportion of catalyst taking part in the polymerisation which effects initiation is suggested as a measure of catalyst efficiency; the hydroperoxides are of moderate efficiency.

The author has shown (*J.*, 1951, 3106; 1952, 2408) that polymerisation data can be used to give information on the decomposition reactions of diacyl peroxides. It seemed desirable to extend this work to hydroperoxides, and to look for regularities between their activity as catalysts in bulk polymerisation and their known activity in emulsion polymerisation.

Eleven hydroperoxides were examined as initiators for the polymerisation of styrene and the data are summarised in Table 1. Except where stated the temperature was 70°, and the catalyst concentration 0·014 mole/l. The symbols and units are those used in the earlier papers: k_i, k_p, and k_t are the rates of initiation, propagation, and termination, respectively; R_c is the rate of catalysed and R_T the rate of thermal polymerisation, C_m is the monomer transfer coefficient, $\bar{P}_n$ the number-average degree of polymerisation; C and M are the concentrations of catalyst and monomer respectively.

TABLE 1.

Hydroperoxide	10^4R_c	10^6k_i	(η)	$10^{-3}\bar{P}_n$	Efficiency (see eqn., p. 1270)
Bu^tOOH	0·285	0·36	1·42	2·60	0·70
$CMe_2Et{\cdot}OOH$	0·44	0·87	1·12	1·88	0·70
$CPhMe_2{\cdot}OOH$	0·49	1·08	0·98	1·57	0·64
$Pr^i{\cdot}C_6H_4{\cdot}CMe_2{\cdot}OOH$ [a]	0·48	1·02	0·91	1·42	0·57
p-$Bu^t{\cdot}C_6H_4{\cdot}CMe_2{\cdot}OOH$	0·39	0·67	1·20	2·06	0·69
p-$C_6H_4(CMe_2{\cdot}OOH)_2$ [b]	0·42	0·74	1·16	1·98	0·70
$C_6H_{10}(OH){\cdot}OOC_6H_{10}(OOH)$ [b]	1·25	6·9	0·45	0·55	0·50
p-Menthane [c]	0·48	1·02	1·16	1·98	0·79
p-Cymene [c]	0·52	1·19	1·00	1·61	0·68
Pinane [d]	0·365	0·65	1·12	1·88	0·60
1 : 2 : 3 : 4-Tetrahydronaphthalene	0·455	0·91	1·10	1·83	0·57

[a] Mainly the p-isomer but some of the m-isomer may be present. [b] These compounds were examined at 0·007 mole/l. to give the same active oxygen concentration as the other peroxides. [c] These compounds could be peroxidised at the $C_{(7)}$ or the $C_{(8)}$ atoms. The latter is more probable, but according to Helberger, Rebay, and Fettback (*Ber.*, 1939, **72**, 1643), the primary $C_{(7)}$ carbon atom of p-cymene is attacked, since on decomposition the hydroperoxide forms cuminaldehyde. [d] This compound is probably the $C_{(1)}$ hydroperoxide. It was examined at 0·0125 mole/l.

Discussion.—The most interesting feature of this group is the relatively small and apparently unconnected variation of polymerisation rates by the different hydroperoxides. *tert.*-Butyl hydroperoxide and 1-hydroxy*cyclo*hexyl 1-hydroperoxy*cyclo*hexyl peroxide [which dissociates in solution to give 1 : 1-bishydroperoxy*cyclo*hexane (Cooper and Davison, *J.*, 1952, 1180)] being excluded, there is a variation of only 25% from the mean. This would imply either that there is little dependence of decomposition rate on structure or that the method is insensitive to such changes. The major change is the increase in rate brought about by substitution of a methyl group in *tert.*-butyl hydroperoxide by an ethyl or an aryl group. It is noteworthy that the two peroxide linkages in *p*-di-(1-hydroperoxy-1-methylethyl)benzene appear to break down independently of one another, and that there is no noticeable increase in the degree of polymerisation resulting from biradical initiation (transfer reactions with the monomer to form mono-radicals may mask any such effect).

The introduction of alkyl substituents into the phenyl group of α-cumyl hydroperoxide is accompanied by a considerable increase in the rate of polymer formation in emulsion polymerisation at low temperatures in the presence of reducing agents. In this system initiation is effected mainly by one-electron addition by a variable-valency ion to the peroxide link (Fordham and Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 4465; 1951, **73**, 1634), and other controlling factors may be the diffusion of hydroperoxide from the monomer to the soap micelles and reaction with the thiol modifier which is usually present.

For these reasons the lack of correspondence between their properties in bulk and in emulsion polymerisation is not unexpected.

The liquid hydroperoxides are difficult to obtain pure. Kharasch, Fono, and Nudenberg (*J. Org. Chem.*, 1951, **16**, 113) have pointed out the great effect of traces of impurities, particularly acids or alkalis, on the rate of decomposition of α-cumyl hydroperoxide. In the present work it was found particularly important to remove all trace of the peroxidation catalyst from the crude hydroperoxide: the effect of small amounts of copper (as the naphthenate) on its ability to initiate the polymerisation of styrene illustrates this (temp. 70°, catalyst concn. 0·014 mole/l.):

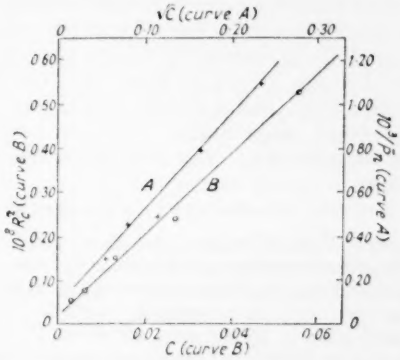
Cu^{++} (mole/l.)	10^4R_c	(η)	Cu^{++} (mole/l.)	10^4R_c	(η)
0	0·49	0·98	0·000125	3·07	0·28
0·000031	2·08	0·32	0·001	4·00	0·15

It is seen that even at the lowest copper concentration over 90% of the hydroperoxide decomposing does so by reactions involving copper ions. The lack of simple proportionality between the copper concentration and the rate of polymerisation indicates that the reactions are very complex.

It was decided to study one of the more readily purified hydroperoxides in greater detail. In the Figure are shown the effects of catalyst concentration on the rate of poly-

merisation and the chain length of the polymer for *p-tert.*-butyl α-cumyl hydroperoxide. The results are plotted as R_c^2 against C and as $1/\bar{P}_n$ against $\sqrt{C}$. They are related to the catalyst concentration by $R_c^2 = R_T^2 + 2k_p^2M^2k_iC/k_t$ and $1/\bar{P}_n = f\sqrt{2k_tk_iC}/k_pM + C_m$ (any reaction of the peroxide with growing polymer chains being ignored at this stage). It follows that the product of the slope of the R_c^2 against C and the square of the slope of $1/\bar{P}_n$ against $\sqrt{C}$ lines will be equal to $4k_i^2f^2$, where f has the value of 1 or ½ depending on whether deactivation occurs by disproportionation or by combination. The actual values give $4k_i^2f^2 = 1{\cdot}77 \times 10^{-12}$ sec.$^{-2}$, whence it follows that $k_i = 0{\cdot}66 \times 10^{-6}$ sec.$^{-1}$ if the chains disproportionate, and $1{\cdot}32 \times 10^{-6}$ sec.$^{-1}$ if combination occurs.*

The former is in excellent agreement with the result calculated from the single experiments, but such internal consistency of the results cannot be taken as evidence for the mode of deactivation. The constants used in the calculation of k_i were based on results which assumed disproportionation to occur. In fact, although the problem has not been finally settled, the overall balance of evidence supports the view that combination is the more likely reaction. [Combination termination with transfer would lead to changes in



Polymerisation of styrene at 70° initiated by p-tert.*-butyl α-cumyl hydroperoxide.*

the polymer distribution from system to system. However, any effect that this may have on the $\bar{P}_n$–(η) relation is probably small since Mayo *et al.* found no significant change in this for polymers prepared thermally (with or without solvents) or with peroxide catalysts; presumably any change in the polymer distribution has an effect which is within their experimental error in establishing the relation from osmotic pressure determinations.]

The effect of temperature on the initiation rates and molecular weights by *p-tert.*-butyl-α-cumyl hydroperoxide (0·014 mole/l.) is shown by the results in Table 2. The rate

TABLE 2.

Temp.	10^5R	10^7k_i	(η)	$10^{-3}\bar{P}_n$	Temp.	10^5R_c	10^7k_i	(η)	$10^{-3}\bar{P}_n$
70°	3·9	6·7	1·20	2·06	49·8°	0·81	0·65	1·70	3·32
60	1·8	2·0	1·36	2·46	30	0·16	0·065	2·30	5·05

constants for the three higher temperatures give a good Arrhenius plot from which $E_i = 28$ kcal./mole. The 30° rate is somewhat high, and is evidently subject to some error, of which there would be a greater probability at such low reaction rates. The corresponding viscosity data have a somewhat small negative temperature coefficient ($E_\eta = -4{\cdot}6$ kcal./mole), which shows that transfer reactions of the growing polymer with monomer and with hydroperoxide are of some importance.

Efficiency of Polymerisation Initiators.—Frequently the data on the reactions of a peroxide in a monomer are not sufficiently detailed or accurate to give full details of its be-

* From the extrapolation of the curve for R_c^2 against C to zero catalyst concentration, $R_T^2 \simeq 0{\cdot}015 \times 10^{-8}$ sec.$^{-2}$. This gives a value for R_T about double that determined directly from the thermal polymerisation. A similar feature was observed and discussed in some detail by Mayo, Gregg, and Matheson (*J. Amer. Chem. Soc.*, 1951, **73**, 1691). Haward and Simpson (*Trans. Faraday Soc.*, 1951, **47**, 212), however, obtained satisfactory agreement between the extrapolated and the measured thermal values.

haviour. It is convenient, however, to estimate the activity of a catalyst quickly from a few results. If it is assumed that there are no secondary reactions, the product of the number-average degree of polymerisation and the rate of polymerisation is given by $1/(K + C_m/R_c)$, where $K = fk_i/k_p^2M^2$. The values of K and C_m for styrene at 70° have been found to be 6·5 and 0·85 × 10^{-4} (Cooper, *loc. cit.*). The efficiency of a catalyst then may be taken as the ratio of the observed product $\bar{P}_nR_c$ from the polymerisation data to the theoretical value given above, *i.e.*,

$$\text{Efficiency} = R_c\bar{P}_n(K + C_m/R_c)$$
$$= 6{\cdot}5R_c\bar{P}_n(1 + 1{\cdot}3 \times 10^{-5}/R_c).$$

With catalysts which produce radicals of high activity this equation gives the ratio of the rates of chain termination and transfer for the ideal to the actual polymerisation reaction. It obviously refers only to the catalyst taking part in the polymerisation and is not necessarily related to the true efficiency as defined by k_i/k_d*.

By using this equation the efficiencies of the hydroperoxides can be calculated from the data in Table 1 and are inserted in the last column of that table. It is seen that the hydroperoxides, apart from the much less stable substituted *cyclo*hexyl peroxide, have comparable efficiencies. For comparison, values for dibenzoyl peroxide [which is the reference compound for all the peroxides, its efficiency being calculated from the decomposition data of Bartlett and Nozaki (*J. Amer. Chem. Soc.*, 1946, **69**, 1686)], di-*m*-nitrobenzoyl peroxide, azodi(*iso*butyronitrile), and *p-tert.*-butylthioazobenzoic acid from this equation are 0·87, 0·31, 0·88, and 0·81, respectively. It is seen that by comparison the hydroperoxides are of relatively low efficiency. This is probably due to their tendency to undergo secondary decomposition.

Experimental

Preparation of Hydroperoxides.—*tert.*-Butyl and *tert.*-amyl hydroperoxides were prepared and purified as described by Milas and Surgenor (*J. Amer. Chem. Soc.*, 1946, **68**, 205, 643). A proportion of the dialkyl peroxide remained in the hydroperoxides used, but it was found that at 70° the dialkyl peroxides have negligible catalytic activity. A fraction of *tert.*-butyl hydroperoxide was used, of b. p. 35°/15 mm., d_{20}^{20} 0·900, n_D^{20} 1·3995 (Found: active O, 16·1. Calc. for $C_4H_{10}O_2$; active O, 17·8%). (The active oxygen concentrations were determined iodometrically by use of a solution of the hydroperoxide in acetic acid and saturated aqueous potassium iodide at room temperature for 15 min. Under these conditions di-*tert.*-butyl and diamyl peroxides do not liberate iodine.)

tert.-Amyl hydroperoxide, purified through the sodium salt and by distillation, had b. p. 68°/43 mm., d_{20}^{20} 0·910, n_D^{20} 1·4145 (Found: active O, 15·0. Calc. for $C_5H_{12}O_2$: active O, 15·4%). α-Cumyl hydroperoxide was prepared by oxidation of cumene by gaseous oxygen in the presence of copper naphthenate. The conditions for efficient peroxidation by this method are rather critical, but the following method was found to be satisfactory. Dry oxygen was circulated by a pump through cumene (1 l.) kept at 45° and containing copper naphthenate (1 g.). The normal induction period was reduced to a very short time by addition of 1% of previously peroxidised cumene containing copper naphthenate. Peroxidation then occurred smoothly at 0·5% per hour for 48 hours. At this stage the partly peroxidised hydrocarbon was washed thoroughly with dilute hydrochloric acid and then potassium hydrogen carbonate solution. In order to obtain a stable product it was important to carry out this process very carefully. To the solution was then added, with cooling, 40% aqueous sodium hydroxide (300 g.). The homogeneous solution gradually set to a mass of crystals. After being collected, washed with light petroleum (b. p. 40—60°), and air-dried, they were decomposed with cold 5N-hydrochloric acid. (Analysis then showed 65% of $CPhMe_2{\cdot}O{\cdot}ONa$, so the crystals are evidently hydrated.) The organic layer, after being washed with potassium hydrogen carbonate solution and water, was dried ($MgSO_4$); the yield was 85% (350—370 g.) of 90—95% pure hydroperoxide, the purity depending on the efficiency of washing of the sodium salt.

* The only hydroperoxides for which decomposition rates have been determined are tetrahydronaphthyl hydroperoxide (Waters, *J.*, 1948, 1579), α-cumyl hydroperoxide (Fordham and Williams, *Canadian J. Res.*, 1949, **27**, *B*, 943; Karasch *et al.*, *loc. cit.*), and *p-tert.*-butyl α-cumyl hydroperoxide (technical data sheet, Phillips Petroleum Co., U.S.A.): values of k_d calculated from these results are of the same order as the estimates of k_i made here, but they are insufficient for any true comparison to be made.

The amounts of catalyst and the temperature were found to be very important. Copper, cobalt, and manganese naphthenates were studied, the efficiency of the reaction varying from 5 to 56% on total oxygen absorption, but the best results (with a reasonable reaction rate) were obtained with the conditions given above.

Fractionation of the residual liquid gave recovered cumene (580 ml.), αα-dimethylbenzyl alcohol (100 g.), and a small amount of 2 : 3-dimethyl-2 : 3-diphenylbutane, m. p. 115° (formed by combination of some of the α-cumyl radicals formed during the peroxidation).

α-Cumyl *iso*propyl hydroperoxide (purity 96%) was prepared and isolated in a similar way to α-cumyl hydroperoxide. *p-tert.*-Butyl α-cumyl hydroperoxide was also obtained by using the above method. The crude hydroperoxide recrystallised from light petroleum (b. p. 40—60°) as colourless needles, m. p. 73° (Found : active O, 7·6. Calc. for $C_{13}H_{20}O_2$: active O, 7·7%). 1 : 2 : 3 : 4-Tetrahydro-1-naphthyl hydroperoxide was prepared by oxidation with air at room temperature of carefully purified tetralin (100 ml.) containing 0·1% of cobalt naphthenate. The crude hydroperoxide obtained *via* the sodium salt was extracted with warm light petroleum (b. p. 40—60°). The extracts at 0° gave needles, which were recrystallised several times from alcohol–carbon tetrachloride (yield 13 g. ; m. p. 54°) (Found : active O, 9·7. Calc. for $C_{10}H_{12}O_2$: active O, 9·75%).

1-Hydroxy*cyclo*hexyl 1-hydroperoxy*cyclo*hexyl peroxide, m. p. 78°, was made as described by Cooper and Davison (*loc. cit.*). *p*-Cymene and *p*-menthane hydroperoxides were obtained as *ca.* 25% solutions of the crude oxidation products. As the gelatinous sodium salts were too soluble to be isolated directly, the solutions were first concentrated at 12 mm. to about 60% hydroperoxide content. After being washed repeatedly with light petroleum (b. p. 30—40°), the sodium salts gave on decomposition hydroperoxides of 99% and 98·5% purity, respectively.

p-Di-(1-hydroperoxy-1-methylethyl)benzene, recrystallised from benzene–light petroleum (b. p. 40—60°), had m. p. 141° (Found : active O, 13·7. Calc. for $C_{12}H_{18}O_4$: active O, 14·1%). Pinane hydroperoxide, from the Hercules Powder Co., U.S.A., was of 78% purity.

The methods used for obtaining the polymerisation data have been described in the earlier papers (*locc. cit.*).

The author thanks Dr. H. L. Williams of Polymer Corporation, Sarnia, Canada, for several of the hydroperoxides, and the Dunlop Rubber Co. Ltd. for permission to publish this paper.

Chemical Research Division, Dunlop Research Centre,
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254. *The Oxidation of* n-*Paraffins from Propane to Nonane by Nitrous Oxide.*

By E. J. Smith.

An exploratory study of the slow oxidation of propane and other *n*-paraffins up to nonane has been made. The reactions are chain processes involving alkyl radicals; in typical cases they are inhibited by small amounts of nitric oxide and by reaction products. The latter effect is doubtless due to the presence of olefins produced in the simultaneous hydrocarbon pyrolysis both by direct unimolecular breakdown and by thermal decomposition of intermediate alkyl radicals. These stable pyrolysis products are not readily attacked by nitrous oxide at 550° and their formation limits the extent of the oxidation, especially with the higher members of the series. Some tentative conclusions regarding the mechanism of the oxidation are given.

The slow oxidation of hydrogen (Melville, *Proc. Roy. Soc.*, 1933, **142**, *A*, 524; 1934, **146**, 737) and methane (Robinson and Smith, *J.*, 1952, 3895) by nitrous oxide are chain reactions in which oxygen atoms arising from thermal decomposition of the oxide initiate the processes by the respective steps, $H_2 + O \longrightarrow OH + H$, $CH_4 + O \longrightarrow CH_3 + H$. The work on hydrocarbons is being continued by Dr. P. L. Robinson, and this paper describes exploratory observations on the corresponding oxidation of propane and other paraffins up to *n*-nonane. Interesting differences from the behaviour of methane have been observed which are undoubtedly related to the fact that at the temperatures employed (500—600°) all these hydrocarbons are " cracked," producing shorter saturated hydrocarbons (prin-

cipally methane and ethane), olefins, and hydrogen. These pyrolyses are well known as sources of alkyl radicals and involve, simultaneously, free-radical chain and non-chain molecular mechanisms (Stubbs and Hinshelwood, *Proc. Roy. Soc.*, 1950, *A*, **200**, 458; **201**, 18; Ingold, Stubbs, and Hinshelwood, *ibid.*, 1950, **203**, 486; **208**, 285). Both modes of decomposition appear to give the same products in practically the same proportions. The present work suggests that both have an important bearing on the behaviour of the hydrocarbon towards nitrous oxide.

The molecular products, in typical cases, have been shown to react very slowly with nitrous oxide; but the alkyl radicals simultaneously produced must react readily, initiating a cycle terminating in the production of carbon monoxide, carbon dioxide, and water vapour.

Experimental

Materials.—The hydrocarbons used, with the exception of the propane, were presented by Imperial Chemical Industries Limited through the courtesy of Dr. Holroyd. The purity of the *n*-octane and *n*-pentane is given as 90—95%, and that of the remainder as better than 99%. The only further treatment they received was a thorough degassing in the apparatus. The propane, from a cylinder, was washed with pyrogallol, dried, and condensed at −180°; large head and tail fractions were rejected and the remainder given three bulb-to-bulb distillations. Nitrous oxide was taken from a cylinder and treated as described by Robinson and Smith (*loc. cit.*). Nitric oxide, prepared from copper and nitric acid, was freed from nitrogen dioxide with 30% sodium hydroxide, dried, and condensed at −180°. The frozen product was pumped free from nitrogen and distilled several times to rid it of nitrous oxide. The purified nitric oxide was stored in a cooled trap attached to the quenching bulb of the apparatus.

Apparatus.—The apparatus used in the methane work (*loc. cit.*) was modified for work with less volatile hydrocarbons above pentane. The mixing bulb *E* was enveloped in a steam-jacket, and all adjacent leads and taps were also kept at 100° by resistance heating and asbestos lagging. After being outgassed, the hydrocarbons were vaporised from trap *I*, and the required pressure of nitrous oxide was admitted afterwards. Taps between the storage section and reaction vessel were lubricated with silicone grease. Mixtures of the gaseous hydrocarbons with nitrous oxide were prepared in a series of 3-l. bulbs attached to the line and furnished with individual mercury manometers.

Results.—The oxidations proceed at a convenient rate at 500—600° and can be approximately represented by the stoicheiometric stages:

$$(a)\quad C_nH_{2n+2} + (2n + 1)N_2O \longrightarrow nCO + (n + 1)H_2O + (2n + 1)N_2$$

$$(b)\quad CO + N_2O \longrightarrow CO_2 + N_2$$

Since the decomposition of nitrous oxide alone is very slow at these temperatures, the extent of the reaction, expressed in terms of $(CO + CO_2)$ and the other products shown above, may be calculated from the pressure change in the closed vessel. Table 1 gives data for 585° showing the amounts of carbon monoxide and dioxide found by analysis after complete reaction, as well as values for the total carbon oxides, calculated from the pressure increase on the basis of the above reactions. All are expressed as percentages of the gaseous contents of the reaction vessel after removal of water vapour.

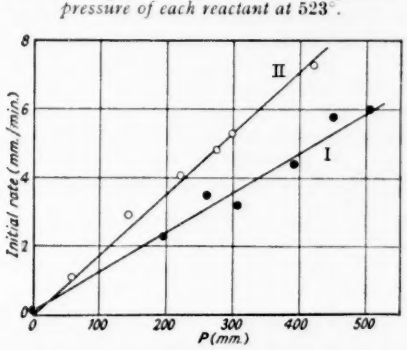
Table 1.

Hydrocarbon	P_{Hy} (mm.)	P_{N_2O} (mm.)	ΔP_∞ (mm.)	$(CO + CO_2)$, %, calc.	CO, % found	CO_2, % found	$(CO + CO_2)$, % found	% of hydrocarbon finally oxidised
Propane	21	226	112	19·7	1·87	19·2	21·1	88·9
n-Pentane ...	20	338	148	18·0	0·3	19·3	19·6	74
n-Nonane ...	15	407	91	12·2	1·03	11·3	12·3	33·7

As with methane, little carbon monoxide remains at the end of the reaction although it is relatively abundant in the earlier stages. In a duplicate run with 19 mm. of propane and excess of nitrous oxide the amounts of carbon monoxide and dioxide found for the semi-completed reaction ($\Delta P = 52$ mm.) were 5·3% and 3·8% respectively. Clearly, carbon monoxide is a primary oxidation product and is further oxidised in the subsequent stage (*b*). Table 1, col. 9, gives the percentage of hydrocarbon oxidised finally, as calculated from ΔP_∞, the reaction being assumed to be completed when no measurable pressure change occurred in 20 min. Any subsequent creep in pressure is attributable to side reactions among the products or to de-

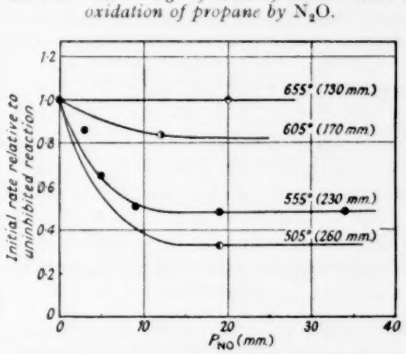
composition of residual nitrous oxide. The diminishing extent of the oxidation on ascent of the homologous series is very striking. A reason for this incomplete oxidation is the concurrent formation by thermal decomposition of the hydrocarbon, of products which are either not readily oxidised themselves or which actively inhibit the oxidation process by removing radicals responsible for its propagation. For example, propylene, an established inhibitor, is produced in the pyrolysis of butane and higher paraffins. Confirmation that this side-decomposition could explain incomplete oxidation was obtained by experiments on *n*-nonane and *n*-pentane: 34 mm. of *n*-nonane were heated at 525° for some hours during which the pressure rose to 61 mm.; 270 mm. of nitrous oxide were then added and the pressure rose at a rate of 0·25 mm./min. This is slow compared with the 8·5 mm./min. given by a mixture of 60 mm. of fresh *n*-nonane with 240 mm. of nitrous oxide at the same temperature. On another occasion, 100 mm. of a 1 : 4 mixture of *n*-pentane and nitrous oxide were heated for 4 hours at 525°; the initial rate of pressure change was 15 mm./min. Afterwards some of the material was removed from the reaction vessel, leaving a pressure of 140 mm., and to this were added 100 mm. of fresh mixture. The initial rate was now 9 mm./min. and had thus been reduced by 40% owing to inhibition by olefins formed in the previous run. Steacie and MacDonald (*Canad. J. Res.*, 1935, **12**, 711) have similarly observed that the reaction between ethylene and nitrous oxide (involving decomposition, polymerisation, and oxidation of the olefin) was slow at 530°.

FIG. 1. *Dependence of initial rate on partial pressure of each reactant at 523°.*



I, P_{N_2O} variable, $P_{C_3H_8} = 50$ mm.
II, $P_{C_3H_8}$ variable, $P_{N_2O} = 50$ mm.

FIG. 2. *Inhibiting influence of nitric oxide on oxidation of propane by N_2O.*



(1 : 3 mixtures): pressures as stated.

The decrease in the completeness of oxidation on passing from propane to *n*-nonane is understandable because of the increasing proportion of molecular, *i.e.*, non-chain, decomposition on ascent of the homologous series. Inhibition studies (Stubbs and Hinshelwood, *loc. cit.*) have shown that the "apparent chain length" for paraffin decomposition (a measure of the proportion of molecules decomposing by a chain path) is 10·0 for propane, 5·0 for pentane, and 3·7 for *n*-nonane at 530° and 100 mm.

Kinetic Measurements with Propane.—In the curves (Fig. 1) the rates are from the initial slopes of pressure–time curves and have been corrected for simultaneous non-chain pyrolysis of the hydrocarbon. Stubbs and Hinshelwood's data were used for this purpose, the maximum correction applied at the highest propane pressure being 5%. The results point to a first-order reaction with respect to each reactant, and suggest a rate equation of the form $dp/dt = k_1[C_3H_8] + k_2[C_3H_8][N_2O]$. The measurements are limited to pressure only, and it is by no means necessary that the rate-determining stage remained exactly the same over the wide range of relative concentrations used. Hence it is unsafe to draw detailed conclusions. Qualitatively, however, the fact that the rate is more sensitive to the hydrocarbon concentration than to the nitrous oxide concentration presents an interesting contrast with methane where the rate depends almost upon the square of the nitrous oxide concentration. It implies, as might be expected from the lower temperature, that initiation is not as before through oxygen atoms. Alkyl radicals, readily formed in the thermal decompostion of propane at this temperature, can now initiate the oxidation sequence. The first term in the rate equation supports this view of initiation *via* propane.

Inhibition Experiments.—It is suggested that olefins simultaneously formed by hydrocarbon decomposition reduce the amount of hydrocarbon oxidised by removing free radicals and

starting a competing polymerisation process. Nitric oxide is more effective than olefins in removing alkyl radicals, and the influence of small quantities upon a standard 1 : 3 mixture of propane and nitrous oxide was studied. Various pressures of highly purified nitric oxide were added to the standard mixture, and their influence on the reaction rate was determined. Control experiments without nitric oxide were performed before and after each run to prove that the

TABLE 2. *Initial rates of hydrocarbon consumption during oxidation at 525° (mm./min.).*

Hydrocarbon	$P_{initial}$ = 100 mm.	$P_{initial}$ = 300 mm.	Hydrocarbon	$P_{initial}$ = 100 mm.	$P_{initial}$ = 300 mm.
Propane	0·133	0·79	*n*-Octane	0·27	0·77
n-Butane	0·12	0·60	*n*-Nonane	0·16	0·47
n-Pentane	0·16	0·95	2 : 2 : 4-Trimethylpentane (" *iso*octane ")	0·2	0·48
n-Heptane	0·32	0·93			

inhibition was real. Fig. 2 shows, for various pressures of nitric oxide and at several temperatures, the rates relative to that of the uninhibited reaction. The curves for 505°, 605°, and 655° involve the assumption that a maximum interference occurs when 20 mm. of nitric oxide are present.

At the lower temperatures nitric oxide has a marked retarding effect on the oxidation, which is taken as confirming the presence of alkyl radicals. This effect decreases at higher temperatures and vanishes above 655°. The residual reaction would normally be attributed to a concurrent non-chain decomposition reaction; but this could hardly account for its magnitude here which is 12 mm./min. at 555°, and a non-chain oxidation process cannot be envisaged. The

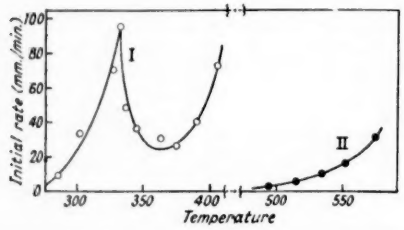


FIG. 3. *Temperature dependence of initial rate of oxidation of propane.*

I, $C_3H_8 : O_2 = 1 : 3$, pressure 410 mm. (maximum rates).
II, $C_3H_8 : N_2O = 1 : 2$, pressure 400 mm.

explanation is to be sought either in a reaction involving the product of the radical–nitric oxide step, or, more probably, in the catalytic influence of nitric oxide on the decomposition of nitrous oxide, leading to additional initiation *via* oxygen atoms. Hinshelwood and Musgrave (*Proc. Roy. Soc.*, 1932, *A*, **135**, 23) have demonstrated the powerful catalytic influence of nitric oxide in promoting the decomposition of nitrous oxide.

Activation Energies.—The activation energies for the oxidation of propane, *n*-butane, and *n*-pentane were deduced from rate measurements with standard mixtures at four individual temperatures and were respectively 44, 45, and 47 kcals. The apparent gradation could suggest a common step in the mechanisms, whose activation energy is subject to some structural influence, and may be signiflcant. Without more knowledge of the probable steps in the mechanisms further speculation is unwarranted.

The absence of any complex temperature-dependence in the oxidation of propane by nitrous oxide is shown by Fig. 3, which contrasts the behaviour of a standard propane–oxygen mixture. The latter exhibits the pronounced " low-temperature " reaction generally attributed to branching chains involving peroxides. This should be precluded in the nitrous oxide combustion and the lower curve confirms this.

Dependence of the Rate of Oxidation on the Hydrocarbon Structure.—Table 2 shows rates of oxidation of a series of normal paraffins under standard conditions, *viz.*, a 1 : 4 mixture of hydrocarbon and nitrous oxide at 525° and at two initial mixture pressures. In deriving the rates, the initial rates of pressure change were each multiplied by a factor $1/2n$, where n is equal to the number of carbon atoms in the particular hydrocarbon, in accordance with the stoicheiometry previously stated. A correction was also introduced for the decomposition of the hydrocarbon by the molecular side reaction, Hinshelwood and Stubbs's data being used. The oxidation rate is seen to increase as the hydrocarbon chain lengthens, and after reaching a maximum, decreases again beyond heptane. As a matter of interest 2 : 2 : 4-trimethylpentane was tested for comparison with isomeric *n*-octane, and a pronounced drop in rate was observed on passing from the straight to the branched skeletal chain.

Discussion

The experimental work described is in the nature of a preliminary survey and the conclusions are accordingly tentative. Reasons have been given indicating that the oxidation of paraffin hydrocarbons by nitrous oxide involves alkyl radicals, and since pyrolysis of the hydrocarbons occurs readily at the temperatures employed, these radicals must be formed at an early stage of the reaction. It is convenient to summarise the main steps in the decomposition chain reaction in view of the probable connection of this with the oxidation process. These are as follows (see Steacie, "Atomic and Free Radical Reactions," 1946): (i) Initial breakage of a C–C bond in the hydrocarbon molecule, forming two alkyl radicals; rupture occurs predominantly in the positions $\overset{1}{\text{C}}\text{–}\overset{2}{\text{C}}\text{–}$ and $\text{C}\text{–}\overset{2}{\text{C}}\text{–}\overset{3}{\text{C}}\text{–}$. (ii) Hydrogen abstraction from a fresh hydrocarbon molecule by radical attack; this produces a saturated compound such as methane or ethane and a larger alkyl radical. (iii) Thermal decomposition of alkyl radicals to yield olefins and smaller radicals or hydrogen atoms; fission occurs more readily at the C–C bonds than at the stronger C–H bonds, as Bywater and Steacie (*J. Chem. Phys.*, 1951, **19**, 172, 319) have shown in the case of propyl and butyl radicals. The methyl radical, which can only decompose by rupture of C–H bonds, is stable up to 900°.

Process (i) appears to provide the most feasible initiation step for the oxidation process also, since oxygen atoms are not formed from nitrous oxide at the temperatures used, and the direct bimolecular step $RH + N_2O \longrightarrow R + OH + N_2$ requires the simultaneous rupture of two bonds. The oxidation mechanism could then feasibly proceed by the formation of alkoxy-radicals in the step (iv) $R + N_2O \longrightarrow RO + N_2$ and their subsequent breakdown to aldehyde and simpler fragments in the established manner (Bell, Raley, Rust, Seubold, and Vaughan, *Discuss. Faraday Soc.*, 1951, **10**, 242). The final stable oxidation products probably arise from further oxidation stages, whose elucidation has not been attempted here.

The increasing rate of oxidation on passing from propane to *n*-heptane resembles the similar trend observable in the decomposition rate and (although to a much greater degree) in the rate of oxidation of *n*-paraffins by molecular oxygen. Such effects are attributable *inter alia* to increasing ease of initial rupture of the skeletal chain, and of hydrogen-atom removal in radical attack, as the hydrocarbon chain length increases.

In considering the reasons for reversal of this trend in the cases of *n*-octane and *n*-nonane, one should note the very low percentage of hydrocarbon returned as carbon oxides when *n*-nonane was allowed to react completely with nitrous oxide (Table 1). This cannot be entirely accounted for by the simultaneous molecular decomposition of the hydrocarbon into non-oxidisable substances; the decomposition of large alkyl radicals by process (iii) must be responsible for some of the olefins formed. Hence, unimolecular decomposition of radicals must always compete to some extent with their bimolecular removal by nitrous oxide in (iv), and since in the former process one of the products is a stable molecule not readily oxidised, such decomposition will tend to decrease the rate of the overall oxidation process. Radicals larger than methyl are increasingly stabilised by resonance, especially when the chain is branched (Baughan, Evans, and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 377), and the activation energy of processes such as (iv) could therefore be expected to increase and lead to a relatively greater loss of radicals by unimolecular breakdown as the hydrocarbon chain length increases. This retardation, coupled with gradual simultaneous decrease in the previous accelerating influences, seems to offer at least a qualitative explanation of the observed decrease in oxidation rate beyond *n*-heptane. The large decrease observed for 2 : 2 : 4-trimethylpentane is in accordance with this explanation in view of the enhanced resonance stabilisation of branched-chain radicals.

I thank Dr. P. L. Robinson for suggesting this survey, and for advice and encouragement. Acknowledgment is also made to the Department of Scientific and Industrial Research for a maintenance grant during the tenure of which this work was commenced.

King's College, Newcastle-on-Tyne, 1. [*Received, November 27th*, 1952.]

255. *The Electronic Structures and Spectra of Some Molecules related to Oxygen.*

By L. E. Orgel.

The electronic structures and spectra of nitroso-compounds, nitrites, and azo-compounds are discussed in relation to those of the oxygen molecule. It is shown that the diamagnetism of these compounds and their spectra can be interpreted in terms of a simple perturbation treatment of the oxygen molecule.

Electronically, the nitroso-compounds and azo-compounds are closely related to oxygen. In this paper their spectra and electronic properties are discussed in the light of this relationship.

The ground state of oxygen is a $^3\Sigma_g^-$ state arising from the electronic configuration $(\sigma_g 2s)^2 (\sigma_u 2s)^2 (\sigma_g 2p)^2 (\pi_u 2p)^4 (\pi_g 2p)^2$. The other states arising from this configuration are $^1\Delta_g$ and $^1\Sigma_g^+$ located at 0·98 ev and 1·63 ev respectively above the ground state. The next observed states, about 4 ev above the ground state, are $^3\Sigma_u^+$ and $^3\Sigma_u^-$ arising from the configuration $(\pi_u 2p)^3 (\pi_g 2p)^3$.

The wave-functions for the states arising from the lowest configuration are given by Moffitt (*Proc. Roy. Soc.*, 1951, **210**, *A*, 224). It is convenient to write them in a slightly different form. We define an xz plane containing the O–O axis, the latter being in the direction of the x-axis. If π_z and π_y are the components of the degenerate, antibonding π_g orbital which are parallel and perpendicular to the xz plane then, filled shells being neglected, the wave-functions are:

$$\Psi^3\Sigma_g^- [\pi_z(1)\,\pi_y(2) - \pi_z(2)\,\pi_y(1)] \begin{cases} [\alpha(1)\,\alpha(2)] \\ [\alpha(1)\,\beta(2) + \alpha(2)\,\beta(1)] \\ [\beta(1)\,\beta(2)] \end{cases}$$

$$\left.\begin{array}{l} \Psi^1\Delta_g\,[\pi_z(1)\,\pi_y(2) + \pi_z(2)\,\pi_y(1)] \\ \Psi'^1\Delta_g\,[\pi_z(1)\,\pi_z(2) - \pi_y(1)\,\pi_y(2)] \end{array}\right\} [\alpha(1)\,\beta(2) - \alpha(2)\,\beta(1)]$$

$$\Psi^1\Sigma_g^+ [\pi_z(1)\,\pi_z(2) + \pi_y(1)\,\pi_y(2)] \quad [\alpha(1)\,\beta(2) - \alpha(2)\,\beta(1)]$$

where α and β are spin functions.

If we consider instead of O_2 the isolectronic molecule HNO we would expect changes in the intervals between the $^3\Sigma^-$, $^1\Delta_g$, and $^1\Sigma_g^+$ states, but no changes in the qualitative energy level scheme. The main changes in the π-electron system would come about through the mixing of the $(\pi_u 2p)^4 (\pi_g 2p)^2$ with the $(\pi_u 2p)^3 (\pi_g 2p)^3$ configurations. This, as may be seen by writing out the molecular-orbital functions explicitly, could lead to the concentration of charge at one end of the molecule.

If now we allow the hydrogen nucleus to move off the N–O axis, remaining in the xz plane, we find that the degenerate $^1\Delta_g$ level splits into two components. The $\Psi^1\Sigma_g^+$ and $\Psi'^1\Delta_g$ wave-functions are both symmetrical about the xz plane and hence will be mixed together by the non-axial perturbation of the hydrogen nucleus. A qualitative energy-level diagram showing the dependence of the levels on the displacement of the hydrogen nucleus from the N–O axis is given in the Figure. The $^3\Sigma_g^-$ and $^1\Delta_g$ levels have been drawn as parallel, straight lines. In fact these levels will be affected to different extents by the perturbation, so our procedure is not accurate. The important point is that the $^1\Delta_g$ level is split and may be displaced below the $^3\Sigma_g^-$ level.

These results of a simple theoretical treatment can be explained qualitatively. The displacement of the hydrogen nucleus in the xz plane stabilises the π_z orbital relative to the π_y orbital. This does not greatly alter the energy levels in first-order perturbation theory, since in each case there is one electron in each orbital. However, in second-order perturbation theory the mixing of $\Psi'^1\Delta_g$ and $\Psi^1\Sigma_g^+$ functions leads to a concentration of electrons in the xz plane. This is seen by forming the combination

$$\alpha\Psi'^1\Delta_g + (1 - \alpha^2)^{\frac{1}{2}}\Psi^1\Sigma_g^+$$

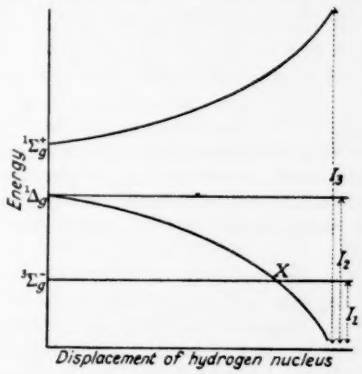
which can be written

$$\{\alpha + (1 - \alpha^2)^{\frac{1}{2}}\}\pi_z(1)\,\pi_z(2) + \{(1 - \alpha^2)^{\frac{1}{2}} - \alpha\}\pi_y(1)\,\pi_y(2)$$

Clearly, if α increases to $1/\sqrt{2}$ we find both of the electrons in the π_z orbital. This crowding of electrons into the xz plane is opposed by the interelectronic repulsions. As the hydrogen nucleus is displaced from the N–O axis the perturbation becomes larger compared with the inter-electronic repulsions, and the electrons become more concentrated in the xz plane. Sooner or later the energy of the stabilised state becomes greater than that of the $^3\Sigma_g^-$ state and the energy levels cross. After this point the ground state is a singlet.

After the crossing point X (see Fig.), the $^3\Sigma_g^- - ^1\Delta_g$ transition of oxygen should be replaced by a singlet–triplet transition shown as I_1, and a new singlet–singlet transition I_2 should appear. Of course the angular momentum about the N–O axis is no longer quantised, so descriptions such as Σ and Δ lose their significance. The considerations of the previous paragraph show that the upper states of these transitions have approximately equal densities of π-electrons in and perpendicular to the xz plane, while in the ground state both of the original π_g electrons are in the xz plane; *i.e.*, the $^3\Sigma_g^- - ^1\Delta_g$ transition of oxygen is replaced by what is conventionally termed a σ–π transition, and also a new singlet–singlet σ–π transition I_2 appears. The transition I_3 becomes more and more like a two-electron transition and hence should be very weak.

If we make the reasonable assumption that the N–H group is less electronegative than the oxygen atom, we may expect the electron transferred in these transitions to come



Qualitative energy level diagram for the H–N–O *system, showing the effect of displacing the hydrogen atom from the* N–O *axis.*

largely from the nitrogen atom. Our final description of the transitions would be as unshared pair-antibonding orbital, σ–π transitions.

Little is known about the molecule HNO, but all our considerations should apply with little change to the systems RNO, where R is an aliphatic, aromatic, or other univalent radical. The physical properties of aliphatic and aromatic nitroso-compounds have been studied. The monomeric molecules are diamagnetic, showing that the singlet state has been displaced beneath the lowest triplet. Their blue or green colours are found to result from rather weak absorption bands which extend some way into the infra-red (Lewis and Kasha, *J. Amer. Chem. Soc.*, **1945**, **67**, 997). Lewis and Kasha claim that this band, which in typical cases begins at about 1·7 ev, is a singlet–triplet transition. If this is true it may be identified with the transition I_1 of the figure. In view of the rather high intensity, however, it seems quite possible that it is in fact the transition I_2, an assignment which is not ruled out by Lewis and Kasha's evidence. In either case the displacement of the singlet level is not less than 1·7 ev compared with the 0·65 ev separating the $^1\Delta_g$ and $^1\Sigma_g^+$ states of oxygen. This shows that the structure with both electrons in the RNO plane does predominate. Rough calculations suggest that the configuration with two electrons in the antibonding orbital cannot contribute more than a few units % to the wave-function or more than 1% in weight to the final structure.

The absorption spectra of a number of compounds in which the N–O group is attached to a univalent radical have been measured. The aliphatic and aromatic nitroso-compounds have bands in the visible and near infra-red beginning at about 14,500 cm.$^{-1}$ and 12,000 cm.$^{-1}$, respectively. The corresponding values of $\varepsilon_{max.}$ are about 10 and 50 (Kortum,

Z. Electrochem., 1941, **47**, 55; Hertel and Lebok, *Z. phys. Chem.*, 1940, **47**, *B*, 315). The nitrites and nitrosamines absorb at about 25,000 cm.$^{-1}$ with $\varepsilon_{max.}$ values of 50—70 (Kortum, *ibid.*, 1941, **50**, *B*, 361). Nitrosyl chloride has a very weak absorption with $\varepsilon_{max.}$ <1 at 15,500—17,500 cm.$^{-1}$, followed by a very broad absorption band with a maximum at 30,000 cm.$^{-1}$ and a value of 32 for $\varepsilon_{max.}$ (Goodeve and Katz, *Proc. Roy. Soc.*, 1939, **172**, *A*, 432). It seems probable that all the bands with $\varepsilon_{max.}$ between 10 and 100 arise from the same fundamental transition and this, in the author's view, is likely to be the singlet–singlet σ–π transition. If this is correct the weak band in nitrosyl chloride must be the singlet–triplet transition. Its appearance in this compound can be understood, since the heavy chlorine atom will facilitate multiplicity-forbidden transitions. We would expect that in nitrosyl bromide the corresponding transition would be in much the same position but several times more intense.

The displacement to longer wave-lengths of the main transition in nitrosobenzene is probably due to the conjugation of the excited π-electron with the aromatic system in the upper state. The much larger shift to shorter wave-lengths in the nitrites, etc., is due to the extensive donation of electrons into the antibonding π-orbital from the oxygen unshared pairs which takes place in the ground state. This partial occupation of the antibonding π-orbital is much less favoured in the upper states since it then already contains one electron. Consequently, the ground state is stabilised relative to the excited state and the transition moves to shorter wave-lengths.

If we now replace the oxygen atom of the nitroso-compounds by a second N–R group we obtain an azo-compound. Azomethane vapour has a weak absorption with a maximum at about 25,000 cm.$^{-1}$ and $\varepsilon_{max.}$ 16 (Kirkbride and Norrish, *J.*, 1933, 122). In the aromatic azo-compounds the absorption in this region is often more intense, presumably owing to interactions with the nearby aromatic absorptions. In some of the simpler compounds the absorption is normal, *e.g.* in phenylazomethane $\varepsilon_{max.}$ = 87 (Burawoy, *J.*, 1937, 122). These characteristic azo-bands are probably due to the same σ–π transition displaced to shorter wave-lengths by the extra stabilisation of the π-electrons in the plane of the molecule.

If the azo-molecule is deformed until the N–R bonds lie in perpendicular planes containing the N–N axis, then we would expect the ground state to be a triplet. This should be compared with the similar situation in ethylene.

Formally, we can treat the molecules $CH_2{:}O$, $CH_2{:}NR$, and $CH_2{:}CH_2$ in the same way. Although the σ–π transitions can be detected spectroscopically, the molecules are now so different from oxygen that it seems unlikely that this method can be applied profitably.

The author is indebted to Professor R. S. Mulliken and Professor C. A. Coulson for helpful suggestions.

MAGDALEN COLLEGE, OXFORD. [*Received, December 22nd*, 1952.]

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256. *A Small Laboratory Liquid–Liquid Extraction Apparatus.*

By J. F. SHORT.

A convenient apparatus is described suitable for routine liquid–liquid extraction on the laboratory scale. It is simple to construct and operate and offers distinct advantages over the conventional method of extracting by batch-wise shaking in separatory funnels.

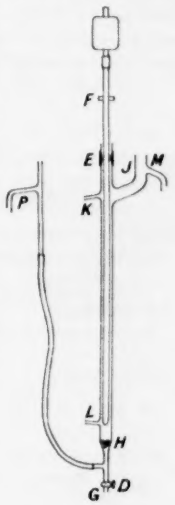
THE extraction of a liquid by an immiscible or comparatively immiscible solvent is normally carried out in the laboratory by the inefficient method of repeated single-stage shakings with fresh lots of solvent; with unfavourable distribution coefficients, this leads to a relatively large bulk of weak extract, and is tedious and time-consuming, particularly where phase separation is difficult. A considerable advantage should be obtained in such operations by use of a counter-current extraction column where a multi-stage separation can be effected in a single pass. Such an apparatus can be operated under conditions which minimise phase-separation difficulties by avoiding extremely fine dispersion.

Most existing types of column are too large and complicated for small-scale application, but one simple type, capable of being scaled down to suitable dimensions, was first described by Jantzen (Dechema Monograph 5, No. 48, p. 114, 1932) and improved by other workers (Ney and Lochte, *Ind. Eng. Chem.*, 1941, **33**, 825; Schutze *et al.*, *Ind. Eng. Chem. Anal.*, 1938, **10**, 675; Shell Development Co., B.P., 615,425/1949; Short and Twigg, *Ind. Eng. Chem.*, 1951, **43**, 2932). In the simple modification now described, the scale has been reduced so as to afford an effective tool for routine laboratory extractions.

The essential feature of the apparatus is a solid cylindrical core rotating inside a coaxial cylindrical column, and the two relatively immiscible liquids pass counter-currently through the annular space. At certain speeds of rotation the liquid motion in the column assumes the form of a stack of horizontal vortex rings, a plainly visible phenomenon investigated mathematically by Taylor (*Phil. Trans.*, 1923, *A*, **223**, 289) and by Lewis (*Proc. Roy. Soc.*, 1927—28, *A*, **117**, 388). The importance of this motion, as applied to extraction, is that the solvent phase traverses a very long path through progressively stronger raffinate as it passes through the column.

Experimental

Apparatus.—The column was made in one piece from a length *EG* of straight glass tubing of fairly uniform bore, as shown in the diagram. Rotors of different diameters were made from straight lengths of glass rod or sealed tubing or of stainless steel, and, when in use, each was mounted in two bearings cut from discs of 3/16" " Tufnol " sheet. One bearing was clamped to the top of the column at *E* by a rubber sleeve, and the other held in a clamp 4—5" above, at *F*. The free end of the rotor was connected by rubber sleeves, by way of a short length of steel rod (to give a measure of flexibility in alignment), to the driving shaft of a 1/30 H.P. variable-speed motor. Owing to the absence of a bearing at the bottom of the rotor, whipping of the latter was pronounced at some speeds of rotation, but this did not appear to affect adversely the efficiency or throughput. Rotor speed was conveniently measured and controlled with the help of a stroboscopic disc mounted on the free end of the motor shaft and actuated by the 50-cycle lighting circuit.



In testing the column, liquids were fed by gravity through small needle valves and rotameters, since this required careful control of flow rates; but for routine operations they could probably be supplied direct from graduated tap-funnels. Lighter phase entered the column at *L* and overflowed at *M* where the " Claisen head " formed a calm space for phase separation when the interphase was at the top. Heavier phase entered at *K* and overflowed at *P*, the level of which could be adjusted to control the position of the interphase in the column. A loose coil of fine-gauge " stainless " steel wire was located at *H* and helped to prevent finely-dispersed lighter phase from being carried out with the heavier effluent. The column could be drained through *D*. Column dimensions are given in Table 1.

Column Operation.—It was important that, with small columns of this kind, the column and rotor should be initially clean and free from grease. With a given extraction system and a given annulus width, there was an optimum rotor speed giving the most efficient extraction.

Table 1. *Column dimensions.*

Mean I.D. of tube = 0·772 cm.; overall length, *EG* = 14½ in.; effective annulus length, *KL* = 11½ in.

Rotor	A	B	C	D
Rotor material	Glass	S/S	Glass	Glass
Rotor mean O.D. (cm.)	0·570	0·476	0·456	0·438
Annulus mean width (mm.)	1·01	1·48	1·58	1·67
Free space in assembled column (ml.)	10·6	13·2	13·5	14·0

This speed occurred in the range where liquid motion in the column assumed the vortex form. The droplet size of the disperse phase was remarkably uniform and decreased with increasing rotor speed. This uniformity of dispersion and the absence of very finely dispersed liquid,

such as is obtained in the normal batch-wise agitation, helped to minimise difficulty in phase separation. The optimum extraction efficiency generally occurred at rotor speeds of 200—300 R.P.M. above the speed at which the vortex rings first developed. The dispersion was then fine enough for good interfacial contact but not so fine as to reduce throughput seriously by hindering phase separation.

With a given extraction system, the efficiency became greater as the annulus was made narrower, but there was a lower limit to the annulus width for the column to function satisfactorily. This limiting width was usually greater with systems having higher interfacial tension. With an annulus narrower than the limiting width there was a tendency for the disperse phase to coalesce into " slugs " which produced poor interfacial contact and restricted throughput, especially if the apparatus was not perfectly clean. By having a range of readily interchangeable rotors of different diameters it was an easy matter to select one suitable for any of the test systems used. Under standard test conditions, repeatable results were obtained, and Table 2 lists a number of results obtained under test conditions in which the solute concentrations ranged from 3 to 5%. In addition to the test runs, successful column operation was obtained in transferring solutes between water and *iso*propyl ether, decane, and amyl alcohol severally. Column performance was assessed in terms of H.E.T.S., or height equivalent to one theoretical or perfect stage, which may be defined as follows: where the degree of extraction attained in a counter-current extraction column of height H is equivalent to that which would be attained in a batch counter-current series of n perfect stages, the H.E.T.S. is H/n.

An interesting factor in Table 2 is the percentage of total solute transferred in a single passage through the apparatus. This is compared with the percentage which would be extracted in a single equilibrium stage with the same phase ratio. In the test runs the degree of stripping was a secondary condition to the determination of H.E.T.S., and with one exception all test runs were made at approximately the minimum theoretical solvent/feed ratio. The exception

TABLE 2. *Test runs with various systems.*

	Continuous phase		Disperse phase					% of total solute transferred in :	
Rotor	Nature	Flow, ml./hr.	Nature	Flow, ml./hr.	Rotor R.P.M.	No. of perfect stages	H.E.T.S., in.	Column	Single stage at same solvent/feed ratio
A	Aq. *cyclo*hexylamine	120	*cyclo*Hexane	60	960	8·0	1·4	91	46
	Aq. acetic acid	67	COMeBu^t	126	960	18·0	0·64	87	50
	COMeBu^t	162	Aq. acetic acid	90	960	4·6	2·5	78	49
	Aq. piperidine	75	C_6H_6	80	580	5·5	2·1	73	49
	"	120	CCl_4	190	1460	3·7	3·1	93	61
B	COMeBu^t	162	Aq. acetic acid	90	1460	3·0	3·8	68	49
	Aq. piperidine	100	C_6H_6	100	960	3·4	3·4	58	48
	Aq. *cyclo*hexylamine	180	*cyclo*Hexane	90	960	1·7	6·8	63	46
C	Aq. piperidine	80	C_6H_6	80	1460	4·3	2·7	74	48
	Aq. maleic acid	100	Bu^{n}OH	90	580	5·8	2·0	87	49
	Water	100	Maleic acid in Bu^{n}OH	100	820	8·5	1·4	82	49
D	Aq. maleic acid	80	Bu^{n}OH	70	820	7·2	1·6	91	48

was in extracting piperidine from water by carbon tetrachloride at a solvent/feed weight ratio of 2·5, the theoretical minimum being 1·6. This minimum is defined as the minimum ratio at which the solute could be stripped completely in an apparatus comprising an infinite number of stages. When it is realised that the outgoing extract cannot exceed a concentration in equilibrium with the ingoing feed, the minimum ratio will be seen to be approximately the inverse of the distribution coefficient where the latter is truly constant. In practice, a ratio 1·5—2 times the theoretical minimum would be employed, but this would be much less than that required to strip the same percentage of solute by successive extractions with fresh solvent.

Better extraction efficiency was usually obtained as flow rates approached the limits at which the column flooded. The flows quoted in Table 2 are near the respective limits and so give an indication of the throughputs to be expected from such an apparatus. Throughputs are generally lower for the rotating-core column than for other types of comparable size, but this is not a serious handicap to their use on a laboratory scale.

By adjusting the level of the movable overflow, either liquid can be made the disperse phase, and in general more efficient extraction will be achieved by dispersing that liquid which is being passed at the higher flow.

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THE DISTILLERS COMPANY, LTD.,
GREAT BURGH, EPSOM, SURREY. [*Received, December 15th*, 1952.]

257. *Geometrical Isomerism of Azo-compounds.*

By NEIL CAMPBELL, ANDREW W. HENDERSON, and DUNCAN TAYLOR.

cis-2 : 2′- and -3 : 3′-Azopyridine have been prepared and their properties studied. Unsuccessful attempts to isolate the *cis*-forms of other azopyridine derivatives are reported. Methods of characterisation included determination of eutectic points with selected second components by means of contact preparations (Kofler, see below), *X*-ray powder photographs, and measurements of dipole moments. Numerous cases of polymorphism are recorded. The thermal behaviour of *cis*-azobenzene is quite different from that of a mixture of azoxybenzene and hydrazobenzene (cf. Hodgson, *J.*, 1948, 1102).

THE evidence from several laboratories is overwhelmingly in favour of the unstable form of azobenzene being *cis*-azobenzene. Hodgson (*J.*, 1948, 1102) does not accept this, however, and states " a double compound of azoxybenzene and hydrazobenzene exhibits far more convincingly many of the reactions of *cis*-azobenzene." Hodgson's objections have been refuted by Le Fèvre (*Chem. and Ind.*, 1948, **26**, 158), Waters (*ibid.*, p. **301**), Bright, Carson, and Dyson (*Research*, 1950, **3**, 185), and Tetlow (*ibid.*, p. **187**). In particular Le Fèvre and Souter (*J.*, 1949, 1595) reported that hydrazobenzene and azoxybenzene form a simple eutectic below 20° and this is in agreement with Hyrnakowski's statement (*Atti 10th Congr. Intern. Chim.*, 1939, **3**, 197) that azoxybenzene and hydrazobenzene form a mechanical mixture. We have confirmed these findings by comparing the melting behaviour on microscope slides of *cis*-azobenzene films in contact along an edge with films of (*a*) azoxybenzene and (*b*) hydrazobenzene, using Kofler's method of contact preparations (Kofler and Kofler, " Mikromethoden zur Kennzeichnung organischen Stoffe und Stoffgemische," Universitätsverlag, Innsbruck, 1949). We found that azoxybenzene and hydrazobenzene do not form a molecular compound, but give a eutectic at 31·5°. *cis*-Azobenzene forms eutectics with hydrazobenzene and azoxybenzene at 58° and 19° respectively. On the other hand *cis*-azobenzene when repeatedly melted and cooled is gradually converted into the stable *trans*-isomer with which it forms a eutectic (40°). The individuality of the unstable isomer was further demonstrated by *X*-ray powder photographs (Unicam 9-cm. camera, Cu-$K\alpha$ radiation), a unique set of spacings being found. Mixtures of azoxybenzene and hydrazobenzene on the other hand, whether melted together or crystallised together from a solvent, gave only those spacings characteristic of the separate components. These results strongly suggest that the unstable azobenzene is the *cis*-isomer.

Le Fèvre (*J.*, 1951, 1814) obtained evidence for the existence of *cis*-2 : 2′-azopyridine. We have isolated the *cis*-compound by irradiating solutions of 2 : 2′-azopyridine with light from a mercury-vapour lamp and separating the products on a column of silica gel. *cis*-2 : 2′-Azopyridine exists as deep-red needles, m. p. 87°, and forms a eutectic with the *trans*-compound at 56°. When the substance is repeatedly heated and cooled, the m. p. falls to 55—57°, and then increases to 83°. The substance then shows no m. p. depression when mixed with a sample of the pure *trans*-isomer.

Absorption spectra also confirm the *cis-trans*-isomerism of 2 : 2′-azopyridine and closely parallel those of *cis*- and *trans*-azobenzene. The azopyridine absorbs at two wavelengths, *trans*- at 314 mμ (log ε 3·97) and 450 mμ (log ε 2·53), and *cis*- at 284 mμ (log ε 3·87) and 446 mμ (log ε 3·03). The comparable figures for azobenzene are : *trans*- 320 mμ (log ε 4·2) and 450 mμ (log ε 2·5), and *cis*- 305 mμ (log ε 3·4—3·5) and 440 mμ (log ε 3·2) (Winkel

and Siebert, *Ber.*, 1941, **74**, 675; Le Fèvre and Wilson, *J.*, 1949, 1106; cf. Le Fèvre and Worth, *J.*, 1951, 1814). No great accuracy is claimed for the *cis*-azopyridine curve as the measurements had to be carried out as rapidly as possible owing to the mobility of the *cis-trans*-equilibrium under the influence of ultra-violet light. About the main features of the curve, however, there is no doubt.

3 : 3′-Azopyridine was likewise obtained both in the *cis*- and the *trans*-form, but here the melting points of the two forms—82° (*cis*) and 140° (*trans*)—differ considerably. The *cis*- is converted into the *trans*-form much more rapidly than with the 2 : 2′-compound. *X*-Ray powder photographs again showed that each *cis*-isomer possessed characteristic spacings.

Unsuccessful attempts were made to isolate the *cis*-forms of 4 : 4′-azopyridine, 3-phenylazopyridine, 2- and 3-*o*-chlorophenylazopyridine, 4 : 4′-dimethyl-2 : 2′-azopyridine, and 5-bromo-2-phenylazopyridine.

Further evidence for the occurrence of *cis*-isomers was obtained from dipole moments, determined with an apparatus described by Henderson and Taylor (*Trans. Faraday Soc.*, 1953, **49**, 92). The values (see Table) for the 2 : 2′- and 3 : 3′-compounds are parallel to those for azobenzene (zero for *trans*, 3 D for *cis*; Le Fèvre and Hartley, *J.*, 1939, 531) and azoxybenzene (1·7 D for *trans*, 4·7 D for *cis*; Gehrckens and Müller, *Annalen*, 1933, **500**, 296). For the other compounds, since the pure *cis*-isomers could not be isolated, only the

Pyridine derivative	Dipole moment (D) *trans*	*cis*	Change in μ after ultra-violet illumination
2 : 2′-Azo	1·77	4·0	—
3 : 3′-Azo	2·40	2·85	—
2-Phenylazo	2·2	—	+0·6
3-Phenylazo	2·3	—	+0·2
4-Phenylazo	2·7	—	−0·1
4 : 4′-Azo	2·0	—	−0·3
4-Methyl-2-phenylazo	2·7	—	+0·4
5-Bromo-2-phenylazo	2·6	—	+0·2
3 : 5-Dibromo-2-phenylazo	1·8	—	+0·2
2-*o*-Chlorophenylazo	2·1	—	+0·8
3-*o*-Chlorophenylazo	2·4	—	+0·3

approximate change in dipole moment after illumination in benzene solution could be evaluated. Le Fèvre and Vine's procedure (*J.*, 1937, 1805) was used, a constant value 0·26 being assumed for β, this being the mean value for eleven solutions of the *cis*- and *trans*-2 : 2′- and -3 : 3′-compounds. [In their equations for the dipole moment, β is defined by $d = d_1(1 + \beta w_2)$ where d and d_1 are the densities of solution and solvent respectively, and w_2 is the weight fraction of the solute.] The individual values of β varied from 0·20 to 0·31, but since all the compounds in the Table are of similar type and since errors in β have only minor importance in the calculation of the dipole moment, the direction of change of the latter after illumination is considered significant. The changes are consistent with *cis*-isomer formation, except possibly for 4-phenylazopyridine and 4 : 4′-azopyridine. However, simple calculations using structures based on the analogous azobenzenes (Robertson and Hampson, *J.*, 1941, 409) show that in these cases a fall in dipole moment on *cis*-isomer formation may in fact be expected owing to the opposing effects of the azo- and ring nitrogen atoms.

A number of our compounds were found to be polymorphous, monotropy greatly predominating over enantiotropy (cf. Campbell, Henderson, and Taylor, *Mikrochem. Mikrochim. Acta*, 1951, **38**, 376). Depending on the stability of the polymorphs, such compounds when examined by the Kofler technique may show several melting points (and eutectic points when in contact with a second component) and this greatly assisted characterisation of the compounds. As second components in the contact preparations, azobenzene, benzil, *p*-nitrophenol, phenylacetic acid and phenacetin were particularly useful. Contact preparations with pairs of azo-compounds revealed many instances of solid solutions, but none involving *cis*-components. With *trans*-components, great similarity of molecular size and configuration was necessary, the methyl groups in the case of 4-methyl-2-phenylazopyridine + 4 : 4′-dimethyl-2 : 2′-azopyridine being enough to disturb the continuous series of solid solutions obtained with the unmethylated compounds.

A general method for the preparation of aromatic azo-compounds is the condensation of nitrosobenzenes with primary aromatic amines in glacial acetic acid. Attempts to condense nitrosobenzene with 2-aminopyridine in this way failed, but syntheses were successful with an alkaline condensing agent. This suggests that these reactions are of the aldol type (cf. Schönberg and Michaelis, *J.*, 1937, 627; Bergmann, *ibid.*, p. 1628).

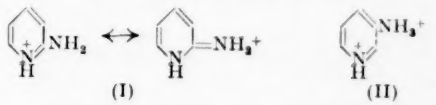
The failure of 2(and 4)-aminopyridine to condense with nitrosobenzene in an acid medium can be attributed to the addition of a proton to the ring-nitrogen atom (see, *e.g.*, Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397; Mann and Watson, *J. Org. Chem.*,

$$C_5H_4N{\cdot}NH_2 + B \rightleftarrows C_5H_4N{\cdot}NH^- + BH^+$$

$$Ph\overset{+}{N}{-}\bar{O} + C_5H_4N{\cdot}\bar{N}H \rightleftarrows Ph{\cdot}\overset{O^-}{\underset{|}{N}}{\cdot}NH{\cdot}C_5H_4N \overset{BH^+}{\rightleftarrows} B + Ph{\cdot}\overset{OH}{\underset{|}{N}}{-}NH{\cdot}C_5H_4N \xrightarrow{-H_2O} Ph{\cdot}N{=}N{\cdot}C_5H_4N$$

(B is a base).

1948, **13**, 502). This results in a positive charge on the 2-amino-nitrogen atom, as in (I), so that interaction with the cation $C_6H_5{\cdot}\overset{+}{N}{\cdot}OH$ is impossible. Such a reason cannot be



(I) (II)

advanced to explain the inertness of 3-aminopyridine in acid solution. It is known, however, that in contrast to its isomers 3-aminopyridine forms dihydrochlorides, etc. Consequently in acid media the amino-nitrogen atom is positively charged, as in (II), and thus does not condense with nitrosobenzene.

Experimental

All the thermal data (m. p.s, eutectic points, etc.) were obtained by means of the Kofler hot-stage microscope (Kofler and Kofler, *op. cit.*).

Preparations of Azopyridines.—(a) Oxidation of aminopyridines by sodium hypochlorite (Kirpal and Reiter, *Ber.*, 1927, **60**, 664) can be used when there is no danger of nuclear chlorination. We confirmed that oxidation of 2-aminopyridine by this method gives **2 : 2′-azopyridine** and a little **5-chloro-2 : 2′-azopyridine** (Kirpal, *Ber.*, 1934, **67**, 70) by purifying the oxidation product by partition chromatography on silica gel. The chloro-compound, m. p. 136°, was quickly washed out, leaving the pure **2 : 2′-azopyridine** at the top. This was eluted with ether–ethanol and crystallised from light petroleum (b. p. 60—80°) in deep red needles, m. p. 85—86°. The method was used to prepare the following substances from the appropriate substituted aminopyridines. **5 : 5′-Dibromo-2 : 2′-azopyridine**, orange needles (from benzene–light petroleum), m. p. 260° (Found: C, 35·0; H, 1·5; N, 16·3; Br, 47·3. Calc. for $C_{10}H_6N_4Br_2$: C, 35·1; H, 1·8; N, 16·4; Br, 46·7%). Bystrikskaya and Kirsanov (*Chem. Abs.*, 1941, **35**, 4023) give m. p. 235° (decomp.). **3 : 3′ : 5 : 5′-*Tetrabromo*-2 : 2′-*azopyridine*** (23% yield) was purified by passing a benzene solution down a column of alumina and separated from benzene in orange needles, polymorphous, m. p. of stable form 103° (Found: C, 24·3; H, 1·7; N, 11·0; Br, 63·0. $C_{10}H_4N_4Br_4$ requires C, 24·0; H, 0·8; N, 11·2; Br, 64·0%). **3 : 3′-Dinitro-2 : 2′-azopyridine** (23% yield), red rhombs (from benzene), m. p. 230° (Found: C, 43·9; H, 2·3; N, 30·5. $C_{10}H_6O_4N_6$ requires C, 43·8; H, 2·2; N, 30·7%). **5 : 5′-*Dinitro*-2 : 2′-*azopyridine*** (41% yield), brownish-red needles (from benzene), m. p. 220° (Found: C, 44·0; H, 2·7; N, 30·9%). **3 : 3′-Azopyridine**, orange needles (from light petroleum), m. p. 140°. **4 : 4′-Azopyridine** (41% yield), orange needles, m. p. 108—109°, after purification on alumina and crystallisation from light petroleum (Found: C, 64·6; H, 4·7; N, 30·2. Calc. for $C_{10}H_8N_4$: C, 65·2; H, 4·4; N, 30·4%). den Hertog and Combe (*Rec. Trav. chim.*, 1951, **70**, 588) give m. p. 104—105°.

(b) *Reduction of nitropyridines by alkaline arsenious oxide.* This method gave **2 : 2′-azopyridine**, m. p. 85—86° (20% yield); **4 : 4′-*dimethyl*-2 : 2′-*azopyridine*** (65% yield), orange needles (from light petroleum), m. p. 149—151°, after purification on alumina (Found: C, 68·0; H, 5·7; N, 26·0. $C_{12}H_{12}N_4$ requires C, 67·9; H, 5·7; N, 26·4%); and **3 : 3′-azopyridine** (62%), m. p. 138—140°.

(c) *Condensation of nitrosobenzenes and aminopyridines.* 2-Aminopyridine (5 g.) was added

to a warm 50% sodium hydroxide solution (50 ml.) which was then gently heated, and benzene (3 ml.) was added. Nitrosobenzene (6 g.) was added during 10 minutes, with shaking, and the mixture warmed for a further 10 minutes. Extraction with benzene (3 × 100 ml.) gave a solution which was heated with charcoal, filtered, and concentrated under reduced pressure to 100 ml. The concentrate was passed down a column of alumina, development of which with benzene gave a lower zone of nitrosobenzene and azoxybenzene, and an orange-red zone which was extracted with benzene. Evaporation afforded **2-*phenylazopyridine*** (8 g.), red needles (from light petroleum, b. p. 40—60°), m. p. 32—34° (Found: C, 72·1; H, 4·7; N, 22·4. $C_{11}H_9N_3$ requires C, 72·1; H, 4·9; N, 22·9%). Similarly nitrosobenzene and the appropriate aminopyridine gave the following: **5-*bromo*-2-*phenylazopyridine*** (86% yield based on the amine), scarlet diamonds, polymorphous, m. p. of stable form 115° (Found: N, 15·8; Br, 30·3. $C_{11}H_8N_3Br$ requires N, 16·0; Br, 30·5%), **3 : 5-*dibromo*-2-*phenylazopyridine*** (84%), crimson plates, polymorphous, m. p. of stable form 112° (Found: N, 12·4; Br, 46·8. $C_{11}H_7N_3Br_2$ requires N, 12·3; Br, 46·9%), **4-*methyl*-2-*phenylazopyridine*** (68%), red prisms, polymorphous, m. p. of stable form 55° (Found: C, 73·1; H, 5·5; N, 21·1. $C_{12}H_{11}N_3$ requires C, 73·1; H, 5·6; N, 21·3%), **3-*phenylazopyridine*** (60%), orange leaflets, polymorphous, m. p. of stable form 52—53° (Found: C, 73·3; H, 4·7; N, 22·4%), and 4-phenylazopyridine (69%), orange leaflets, m. p. 98° (Found: C, 71·6; H, 5·0; N, 23·1%). *o*-Chloronitrosobenzene likewise gives **2-o-*chlorophenylazopyridine*** (48%), red needles, m. p. 54—55° (Found: N, 18·8; Cl, 15·8. $C_{11}H_8N_3Cl$ requires N, 19·3; Cl, 16·3%), and **3-o-*chlorophenylazopyridine*** (47%), red needles, polymorphous, m. p. of stable form 60° (Found: N, 19·7; Cl, 16·8%). The method fails with aminonitropyridines and 2 : 6-diaminopyridine.

Conversion of trans- *into* cis-*Isomers.*—The *trans*-compounds were dissolved in sodium-dried solvents and irradiated by a Hanovia mercury-vapour lamp. Clamping the reaction flask 18 in. from, and 8 in. above, the lamp gave a slight heating effect which mixed the liquid. In a typical experiment azobenzene (5 g.) was irradiated for 12 hours in benzene (250 ml.). The solution was then chromatographed on alumina (diam. 3 in., depth 1½ in.). The chromatogram was developed with benzene until the strongly adsorbed *cis*-layer was separated from the *trans*-compound. Extraction with benzene containing acetone (20 : 1) and evaporation of the extract at low pressure and temperature gave *cis*-azobenzene, rhombic plates (from light petroleum, b. p. 40—60°), m. p. 71° (*lit.*, 71·4°). A sample when melted and cooled afforded broad, flat needles of *cis*-azobenzene followed by smaller needles of the eutectic mixture, m. p. 40°, penetrating in all directions. Alternate heating and cooling caused the temperature of "final melting" (disappearance of last crystals in the melt) to decrease and then rise again, while the melting began consistently at 40°. In this way the final m. p. decreased from 71° to 51° then rose to 66°. The final solidified melt under the microscope showed the absence of eutectic crystals, and the material gave no m. p. depression with a sample of *trans*-azobenzene, m. p. 68°.

cis-m-Nitroazobenzene, m. p. 69—71° (*lit.*, 70°) was repeatedly melted and cooled. The final m. p. sank to 60°, then rose to 94—95°, which was not altered when the substance was admixed with the *trans*-isomer, m. p. 96°. The latter is polymorphic.

cis-p-Iodoazobenzene separated from light petroleum (b. p. 40—60°) in red leaflets, m. p. 74—76°. Repeated melting and cooling caused the m. p. to fall to 62·5° (eutectic point) and then to rise to 99°, which was unaltered when the substance was mixed with pure *trans*-isomer, m. p. 104°. It is suggested that the substance cited in the literature as the *cis*-compound, m. p. 62° (Cook and Jones, *J.*, 1939, 1309) is in fact the eutectic mixture of *cis*- and *trans*-isomers.

Solid *cis-p*-iodoazobenzene is stable and showed no lowering of m. p. after 3 months in the dark.

cis-**2 : 2′-*Azopyridine.*—*trans*-2 : 2′-Azopyridine (2 g.) was irradiated in dry benzene–light petroleum (50 ml.) for 12 hours, then shaken with water, and the non-aqueous solution passed down a column of silica gel (30—40 g. of SiO_2 + 53% of its weight of water in a column 2—5 cm. wide) made up with the same solvent mixture. Development with benzene–light petroleum washed down the *cis*-band, leaving the *trans* as a dull orange layer. The *cis*-solution was evaporated at low temperature and yielded cis-2 : 2′-*azopyridine* (0·25 g.), deep red needles (from light petroleum, b. p. 40—60°), m. p. 87° (Found: C, 65·6; H, 4·3; N, 30·1. $C_{10}H_8N_4$ requires C, 65·2; H, 4·4; N, 30·4%). It forms a mixture with the *trans*-compound, eutectic temperature 56°. Repeated heating and cooling gave the following results:

Disappearance of last crystal (° c)	87	77	80	78	68	67	55	57	75	77	82	84	83	84	83	83	83
Initial melting		75	56	55	50	50	50	38	35	35	35	35	60	55	55	55	

At the final stage the eutectic mixture had practically all disappeared, and the substance showed no m. p. depression when mixed with a sample of pure *trans*-compound. The eutectic value of 35° in some observations can be explained by the assumption that there is a tendency towards polymorphism in either or both the *cis*- and the *trans*-compound.

cis-**2** : **2**′-Azopyridine is almost insoluble in water whereas the *trans*-compound is extremely soluble (cf. Kirpal, *Ber.*, 1934, **67**, 70). It is suggested that the insolubility of the *cis* is due to effective screening of the nitrogen atoms in this configuration. The *trans*-compound gives a deep blue colour with ferrous salts, but the *cis*-compound does not. The *trans*-compound in ethanol gives green and white precipitates with copper sulphate and silver nitrate respectively.

cis-**3** : **3**′-*Azopyridine*.—*trans*-**3** : **3**′-Azopyridine (1 g.) was irradiated as above and the solution passed down a silica gel column (30 × 2 cm.). Development with water-saturated benzene–light petroleum resulted in rapid passage of the *trans*-compound, m. p. 139° (*lit.*, 142°) down the column. The residual orange zone was eluted with benzene–methanol (100 : 1), evaporation of which at low temperature and pressure gave cis-**3** : **3**′-*azopyridine*, scarlet rhombs (from light petroleum), m. p. 82° (Found : C, 65·1; H, 4·5; N, 29·9%). Heating the compound above 100° causes small groups of laths to appear. These grow as the temperature is raised until no liquid is left and then melt at 142°, undepressed when the substance is admixed with the *trans*-compound. Clearly the *cis*- is more quickly converted into the *trans*-compound than is the corresponding **2** : **2**′-compound.

4-*Methyl*-**2**-*nitropyridine*.—2-Amino-4-methylpyridine was oxidised by hydrogen peroxide and sulphuric acid (Kirpal and Bohm, *Ber.*, 1932, **65**, 680) to 4-methyl-2-nitropyridine (36% yield), leaflets (from light petroleum, b. p. 60—80°), m. p. 65·5—66·5° (Found : C, 55·2; H, 4·1; N, 20·4. Calc. for $C_6H_6O_2N_2$: C, 52·2; H, 4·4; N, 20·3%). Wiley and Hartman (*J. Amer. Chem. Soc.*, 1951, **73**, 494) give m. p. 61—62°.

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UNIVERSITY OF EDINBURGH. [*Received, January 12th*, 1953.]

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258. *Phthalaldehydes and Related Compounds. Part II.* Synthesis of* iso*Gladiolic Acid.*

By J. J. BROWN and G. T. NEWBOLD.

The structure of *iso*gladiolic acid, the alkali rearrangement product of gladiolic acid, has been confirmed as 7-methoxy-6-methylphthalide-4-carboxylic acid by synthesis.

THE structure of gladiolic acid (I; R = Me),† an antifungal metabolic product of *Penicillium gladioli* Machacek, has been elucidated by Grove (*Biochem. J.*, 1952, **50**, 648) and Raistrick and Ross (*ibid.*, p. 635). Supporting evidence was obtained by Brown and Newbold (*J.*, 1952, 4878) by examination of 3-formylopianic acid (I; R = OMe) synthesised by treatment of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) with *N*-bromosuccinimide and subsequent hydrolysis.

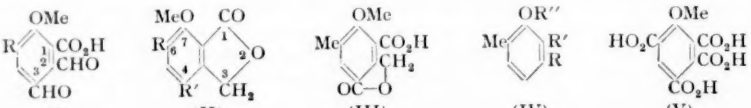
Treatment of gladiolic acid with alkali gives *iso*gladiolic acid, which was formulated by Grove (*loc. cit.*) as (II; R = Me, R′ = CO_2H), though the structure (III), involving lactonisation in the alternative direction, was considered a possibility. Although the alkaline rearrangement product of 3-formylopianic acid (I; R = OMe) was shown to be 4-carboxymeconin (II; R = OMe, R′ = CO_2H) by Brown and Newbold (*loc. cit.*) since it was also formed by oxidation of 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) it was apparent that a synthesis of *iso*gladiolic acid was necessary in order to decide between the possible structures (II; R = Me, R′ = CO_2H) and (III). This has now been carried out.

The synthetical route envisaged required the preparation of 7-methoxy-6-methylphthalide (II; R = Me, R′ = H) as an intermediate. In a first attempt to prepare this

* Part I, *J.*, 1952, 4878.

† For brevity the other, tautomeric form of this structure (see Grove, *J.*, 1952, 3345) has been omitted.

compound 2-hydroxy-*p*-toluic acid (IV; R = CO_2H, R′ = R″ = H)* was reduced by lithium aluminium hydride to 3-hydroxy-4-methylbenzyl alcohol (IV; R = CH_2·OH, R′ = R″ = H); a number of variants of the Kolbe procedure were tried in order to carboxylate the latter compound to the lactone of (IV; R = CH_2·OH, R′ = CO_2H, R″ = H) but all failed to give this product. Attention was then turned to 2-methoxy-*p*-



toluic acid (IV; R = CO_2H, R′ = H, R″ = Me) as starting material. This compound is readily obtained by methylation of 2-hydroxy-*p*-toluic acid (Perkin and Weizmann, *J.*, 1906, **89**, 1649) but was also prepared by carboxylation of the Grignard reagent from 4-bromo-2-methoxytoluene (IV; R = Br, R′ = H, R″ = Me), the latter compound being obtained by methylation of the known 4-bromo-*o*-cresol (Hodgson and Moore, *J.*, 1926, 2036). Simonsen and Rau (*J.*, 1921, **119**, 1339) showed that nitration of (IV; R = CO_2H, R′ = H, R″ = Me) gave 2-methoxy-3-nitro-*p*-toluic acid (IV; R = CO_2H, R′ = NO_2, R″ = Me), the orientation of the nitro-group being proved by conversion of the nitro-acid into 3-nitro-*o*-cresol (Me = 1). The same authors reduced (IV; R = CO_2H, R′ = NO_2, R″ = Me) to 3-amino-2-methoxy-*p*-toluic acid (IV; R = CO_2H, R′ = NH_2, R″ = Me) using ferrous sulphate and ammonia; a more satisfactory reagent for this reaction is sodium hydrosulphite (dithionite). Reduction of the amino-acid (IV; R = CO_2H, R′ = NH_2, R″ = Me) with lithium aluminium hydride gave 2-amino-3-methoxy-4-methylbenzyl alcohol (IV; R = CH_2·OH, R′ = NH_2, R″ = Me) which was diazotised and treated with cuprous cyanide. The nitrile was not isolated in the pure state; the crude product on alkaline hydrolysis gave 7-methoxy-6-methylphthalide (II; R = Me, R′ = H).

Treatment of 7-methoxy-6-methylphthalide with formaldehyde and hydrochloric acid gave a product which we formulate as 4-chloromethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2Cl), the position of the entering group being inferred by analogy with the chloromethylation of meconin (Brown and Newbold, *loc. cit.*); in general the chloromethyl group preferentially enters in the *para*-position to a methoxyl group if this is free and the methoxyl group exerts a much more powerful directive influence than the methyl group, *e.g.*, the reaction of methyl *o*-tolyl ether to give 4-methoxy-3-methylbenzyl chloride (Quelet and Anglade, *Bull. Soc. chim.*, 1937, **4**, 620) and the formation of 6-methoxy-5-methylphthalide from 2-methoxy-*p*-toluic acid (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, **23**, *B*, 17). Hydrolysis of 4-chloromethyl-7-methoxy-6-methylphthalide by aqueous sodium carbonate gave 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), oxidised by dilute, acid potassium permanganate to 7-methoxy-6-methylphthalide-4-carboxylic acid (II; R = Me, R′ = CO_2H) which was identical with *iso*gladiolic acid. (We are indebted to Mr. J. F. Grove, Imperial Chemical Industries Limited, Butterwick Research Laboratories, for the mixed m. p. determination and for comparison of the infra-red spectra of these preparations.)

Grove (*loc. cit.*) oxidised *iso*gladiolic acid to 4-methoxybenzene-1 : 2 : 3 : 5-tetracarboxylic acid (V) whose structure was proved by synthesis; it follows that chloromethylation of 7-methoxy-6-methylphthalide took place in the 4-position. The structure of *iso*gladiolic acid is thus established as (II; R = Me, R′ = CO_2H), and the structure (III) eliminated.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution.

*2-Hydroxy-*p*-toluic Acid* (Me = 1).—2-Nitro-*p*-tolunitrile (50 g.; Pfeiffer, *Ber.*, 1918, **51**, 554) was added in portions with stirring to a solution of stannous chloride (250 g.) in hydrochloric acid (500 c.c.; *d* 1·19) initially at 60°, the temperature being kept below 70°. The mixture

* Toluic acids and cresols are numbered with Me = 1, throughout.

was made strongly alkaline with sodium hydroxide solution (20%) at <40° and extracted with ether (4 × 500 c.c.). The combined ethereal extracts were washed with water (3 × 250 c.c.) and dried (Na_2SO_4); removal of the ether gave 2-amino-*p*-tolunitrile (37 g., 91%), m. p. 77—78°, which was used directly for the next stage [cf. reduction of 2-nitro-*p*-tolunitrile with tin and hydrochloric acid (Borsche and Böcker, *Ber.*, 1903, **36**, 4357) who claim a 50% yield]. 2-Hydroxy-*p*-tolunitrile was prepared from 2-amino-*p*-tolunitrile in 72% yield (*loc. cit.*); no details appear in the literature for its hydrolysis to 2-hydroxy-*p*-toluic acid which was accomplished by heating the nitrile (40 g.) under reflux with sodium hydroxide solution (500 c.c.; 10%) for 4 hours. The solution was acidified with hydrochloric acid (*d* 1·19) to Congo-red and extracted with ether (3 × 250 c.c.). Removal of the ether and crystallisation of the residue from aqueous acetic acid gave 2-hydroxy-*p*-toluic acid (37 g., 80%) as needles, m. p. 205—207° (Meldrum and Perkin, *J.*, 1908, **1416**, gave m. p. 206—207° for the same acid obtained by sulphonation and alkali fusion from *p*-toluic acid).

4-Bromo-2-methoxytoluene.—4-Amino-2-nitrotoluene was converted into 4-bromo-2-nitrotoluene after Gibson and Johnson (*J.*, 1929, 1229) in 70% yield and 4-bromo-*o*-cresol prepared from the latter in 40% yield (Hodgson and Moore, *loc. cit.*). A solution of 4-bromo-*o*-cresol (6·0 g.) in sodium hydroxide solution (30 c.c.; 10%) at room temperature was treated with methyl sulphate (7 c.c.), stirred for 30 min., and then slowly heated to 100° and maintained thereat for 30 minutes. The mixture was steam-distilled until 300 c.c. of distillate had been collected, and *4-bromo-2-methoxytoluene* was isolated by ether as a colourless oil (5·2 g., 80%), b. p. 108°/15 mm., n_D^{16} 1·5632 (Found: C, 48·0; H, 4·7. C_8H_9OBr requires C, 47·8; H, 4·5%). Light absorption: Max. at 210 (ε = 12,000), 222 (ε = 9000), and 276 mμ (ε = 13,000).

*2-Methoxy-*p*-toluic Acid* (Me = 1).—4-Bromo-2-methoxytoluene (10 g.) was added with a crystal of iodine to magnesium turnings (5·0 g.) under dry ether (50 c.c.), and the mixture heated, with stirring, under reflux. A further 26 g. of the bromo-compound in dry ether (100 c.c.) were added dropwise during 2 hours; reflux and stirring were continued for a further 2 hours, most of the magnesium then dissolving. The mixture was cooled to −10° with stirring and a stream of dry carbon dioxide gas directed on the surface at such a rate as to keep the temperature below −2°. When the temperature dropped again an excess of sulphuric acid (25%) was added with cooling, the ethereal layer separated, and the aqueous phase extracted with ether (3 × 50 c.c.). The combined ethereal extracts were washed with sodium hydroxide solution (3 × 50 c.c.; 25%), and the alkaline extract was washed with ether (3 × 25 c.c.), boiled, cooled, and acidified to Congo-red with sulphuric acid (50%). The crude acid was crystallised from aqueous acetic acid, to give 2-methoxy-*p*-toluic acid (57%) as needles, m. p. 156°, undepressed by a specimen, m. p. 156°, prepared by methylation of 2-hydroxy-*p*-toluic acid (Perkin and Weizmann, *loc. cit.*) (Found: C, 65·0; H, 6·1. Calc. for $C_9H_{10}O_3$: C, 65·05; H, 6·1%). Light absorption: Max. at 212 (ε = 55,000), 245 (ε = 20,400), and 292 mμ (ε = 8000).

Demethylation. Anhydrous aluminium bromide (10 g.) in warm dry benzene (60 c.c.) was added to a solution of 2-methoxy-*p*-toluic acid (2·0 g.) in dry benzene (70 c.c.), and the solution refluxed for 4½ hours. Hydrochloric acid (100 c.c.; *d* 1·19) was added to the cooled solution, and 2-hydroxy-*p*-toluic acid (1·7 g.) isolated by ether-extraction, alkali-washing, and acidification. It separated from water (charcoal) as needles, m. p. 207—208°, undepressed by an authentic specimen (Found: C, 63·3; H, 5·5. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3%). Light absorption: Max. at 206 (ε = 46,500), 244 (ε = 12,000), and 298 mμ (ε = 4500).

3-Hydroxy-4-methylbenzyl Alcohol.—Commercial lithium aluminium hydride (10 g.) was refluxed with dry ether for 30 min., cooled to 15°, and treated with a solution of 2-hydroxy-*p*-toluic acid (6·0 g.) in dry ether (200 c.c.) added dropwise during 1 hour, with stirring. The mixture was then refluxed for 3 hours, cooled, and poured on ice. The mixture was acidified (Congo-red) with sulphuric acid (350 c.c.; 4N), and the aqueous phase saturated with sodium chloride and extracted with ether (4 × 200 c.c.) The combined ethereal solutions were washed with water (2 × 50 c.c.), dried (Na_2SO_4), and evaporated. The residual *3-hydroxy-4-methylbenzyl alcohol* crystallised from benzene as needles (4·7 g.; 86%), m. p. 102—103° (Found: C, 69·55; H, 7·5. $C_8H_{10}O_2$ requires C, 69·5; H, 7·3%). The compound sublimed readily at 90°/10^{-3} mm. and had light absorption: Max. at 220 (ε = 6300) and 278 mμ (ε = 2200). Attempts to carboxylate this compound by using potassium hydrogen carbonate in glycerol at 120—130°, 150°, 170°, or 190° for 4 hours with a stream of carbon dioxide were unsuccessful; starting material was recovered at the three lower temperatures and charring occurred at the highest. 3-Hydroxy-4-methylbenzyl alcohol was unchanged after 6 hours at 100° or 24 hours at 130° in an autoclave with water, potassium hydrogen carbonate, and carbon dioxide.

*3-Amino-2-methoxy-*p*-toluic Acid* (Me = 1).—Reduction of 2-methoxy-3-nitro-*p*-toluic

acid, prepared by nitration of 2-methoxy-*p*-toluic acid (Simonsen and Rau, *loc. cit.*), using ferrous sulphate and ammonia, gave a low yield in our hands. The following method proved satisfactory: sodium hydrosulphite (dithionite) (40 g.) was added in portions during 20 min. to a stirred solution of 2-methoxy-3-nitro-*p*-toluic acid (10 g.) in a solution of potassium hydroxide (10 g.) in water (100 c.c.), the temperature being kept below 40°. The solution was made acid (Congo-red) with dilute hydrochloric acid and stored overnight. The solid which separated was crystallised once from water, giving 3-amino-2-methoxy-*p*-toluic acid (7·5 g.) as needles, m. p. 161—162° (lit., 162°).

2-Amino-3-methoxy-4-methylbenzyl alcohol.—Commercial lithium aluminium hydride (2 g.) was heated under reflux with dry ether (70 c.c.) for 30 min., cooled, and treated with 3-amino-2-methoxy-*p*-toluic acid (1·0 g.) in dry ether (70 c.c.) dropwise during 30 min. The mixture was refluxed for 3 hours, cooled, poured on ice, and acidified (Congo-red) with sulphuric acid (90 c.c.; 4N). The solution was then made strongly alkaline with sodium hydroxide and extracted with ether (3 × 50 c.c.). The combined extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated to a dark brown oil which was extracted with boiling light petroleum (b. p. 40—60°) (8 × 50 c.c.). Concentration of the combined extracts to 150 c.c. and storage gave *2-amino-3-methoxy-4-methylbenzyl alcohol* (400 mg.) which separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 48—49° (Found: C, 64·9; H, 7·6. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·8%). Light absorption: Max. at 211 (ε = 26,000), 240 (ε = 6300), and 289 mμ (ε = 2100). The compound sublimed rapidly at 50°/10^{-3} mm.

7-Methoxy-6-methylphthalide.—A solution of 2-amino-3-methoxy-4-methylbenzyl alcohol (400 mg.) in hydrochloric acid (3 c.c.; *d* 1·19) and water (10 c.c.) was diazotised at 0° with sodium nitrite (0·4 g.) in water (5 c.c.). After the addition of urea the filtered solution was added to potassium cyanide (1·6 g.) and copper sulphate (1·4 g.) in water (20 c.c.) at 70°, heated on the steam-bath for 15 min., cooled, and extracted with ether (4 × 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.), dried (Na_2SO_4), and evaporated. The residual oil was heated with potassium hydroxide solution (10 c.c.; 10%) under reflux for 2 hours. The solution was acidified (Congo-red) with hydrochloric acid (*d* 1·19), and the precipitated *7-methoxy-6-methylphthalide* crystallised from water as needles (0·2 g.), m. p. 120° (Found: C, 67·5; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). Light absorption: Max. at 213 (ε = 26,000), 237 (ε = 7500), and 295 mμ (ε = 2800). The compound sublimed rapidly at 80°/10^{-3} mm.

4-Chloromethyl-7-methoxy-6-methylphthalide.—The above phthalide (250 mg.) rapidly dissolved in hydrochloric acid (5 c.c.; *d* 1·19) and aqueous formaldehyde (3 c.c.; 40%) under reflux (45 min.), and an oil separated. The mixture was diluted with water (10 c.c.) and extracted with chloroform (5 × 10 c.c.), and the combined extracts were washed with water (10 c.c.), saturated sodium hydrogen carbonate solution (10 c.c.), and water (10 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave a light yellow gum (250 mg.) which partly crystallised; the solid was separated with the aid of a little methanol and crystallised from ether–light petroleum (b. p. 40—60°) to give *4-chloromethyl-7-methoxy-6-methylphthalide* as needles, m. p. 88—90° (Found: C, 58·6; H, 5·2. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9%). Light absorption: Max. at 216 (ε = 29,400) and 298 (ε = 3000); inflexion at 240 mμ (ε = 7300).

4-Hydroxymethyl-7-methoxy-6-methylphthalide.—The crude chloromethyl compound (200 mg.) obtained after evaporation of the chloroform extract in the previous experiment was heated under reflux with sodium carbonate (0·5 g.) in water (5 c.c.) for 30 min. The solution was made acid (Congo-red) with dilute hydrochloric acid and extracted with chloroform (20 c.c.), and the chloroform extract was dried (Na_2SO_4) and evaporated. The solid residue crystallised from benzene, to give *4-hydroxymethyl-7-methoxy-6-methylphthalide* (150 mg.) as needles, m. p. 119° (Found: C, 63·5; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption: Max. at 212 (ε = 31,000) 238 (ε = 6500), and 298 mμ (ε = 3000). A mixture of the compound with 7-methoxy-6-methylphthalide had m. p. 105—110°.

7-Methoxy-6-methylphthalide-4-carboxylic Acid.—A solution of 4-hydroxymethyl-7-methoxy-6-methylphthalide (50 mg.) in sulphuric acid (25 c.c.; N) at 70° was treated with aqueous potassium permanganate (7 c.c.; 1%). After 10 min. at 70° the solution was decolorised by sulphur dioxide and kept at 0° for 1 hour. The solid was separated and crystallised from aqueous ethanol, to give 7-methoxy-6-methylphthalide-4-carboxylic acid (25 mg.) as needles, m. p. 230—232°, undepressed when mixed with *iso*gladiolic acid (Found: C, 59·7; H, 4·6. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption: Max. at 216 (ε = 33,000) and 298 (ε = 5000) inflexion at 244 mμ (ε = 9000)

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259. *Some Reactions of the Stilbenes in the Presence of Metal Halides.*

By D. S. BRACKMAN and P. H. PLESCH.

Contrary to the claim of Price and Meister (*J. Amer. Chem. Soc.*, 1939, **61**, 1595) neither boron trifluoride nor titanic chloride could be made to isomerise *cis*-stilbene, pure or in solution. Without a co-catalyst there was no reaction; in the presence of a co-catalyst, such as water, *cis*-stilbene polymerised; *trans*-stilbene reacted similarly. Both isomers were polymerised by concentrated sulphuric acid. Experiments in a high-vacuum apparatus showed that both isomers reacted reversibly with titanic chloride to give deep red complexes. The *trans*-stilbene complex was more easily decomposed than the *cis*-stilbene complex and became colourless when cooled in liquid nitrogen; the *cis*-stilbene complex did not. Complex formation did not isomerise *cis*-stilbene. Water, and possibly hydrochloric acid, acted as co-catalysts in the system stilbene–titanic chloride and caused polymerisation of both isomers. The polymers were mixtures of dimers and trimers which included unsaturated compounds, and substituted indanes, but not 1 : 2 : 3 : 4-tetraphenyl*cyclo*butane.

1. *The Isomerisation of* cis-*Stilbene.*—The isomerisation of *cis*-stilbene in carbon tetrachloride solution by boron trifluoride and its ether complex was reported by Price and Meister (*J. Amer. Chem. Soc.*, 1939, **61**, 1595) who stated that both catalysts produced a maximum of 92—93% conversion. In view of the large theoretical superstructure which has been built upon this alleged observation, it seemed pertinent to attempt its reproduction, especially because it could not be confirmed by Downing and Wright (*ibid.*, 1946, **68**, 141). The present authors were unable to isomerise *cis*-stilbene by boron trifluoride. Under dry conditions *cis*-stilbene (pure or in carbon tetrachloride solution) was unaffected by boron fluoride (test by refractive index and ultra-violet spectrum); in the presence of water it polymerised to a tacky resin. Similar results were found with *trans*-stilbene, and with both isomers when titanic chloride was used as the catalyst. These findings are in agreement with those of Meier (*J.*, 1950, 3656) who studied the interaction of boron trifluoride with *cis*-but-2-ene and found that either polymerisation or no reaction at all occurred.

Conditions under which cis-*stilbene has been isomerised.* When *cis*-stilbene was mixed in approximately equimolar proportion with crystalline trichloroacetic acid, a solution was formed which, after three weeks in the dark, gave a purplish crystalline mass. From this, *trans*-stilbene could be isolated. When a hexane solution 0·04M in trichloroacetic acid and 0·4M in *cis*-stilbene was left for 56 hours at room temperature, or refluxed for 3 hours, no *trans*-stilbene was formed.

The isomerisation of *cis*-stilbene by bromine atoms described by Kharasch, Mansfield, and Mayo (*J. Amer. Chem. Soc.*, 1937, **59**, 1155) and by iodine and ultra-violet light, reported by Zechmeister and McNeely (*ibid.*, 1942, **64**, 1919), was confirmed. We found that *cis*-stilbene neither isomerised nor polymerised when kept for a week at room temperature over floridin activated at 300° for 2 hours. Lebedev and Filonenko (*Ber.*, 1925, **58**, 163) found that molten *trans*-stilbene is not polymerised by activated floridin.

Polymerisation of cis- *and* trans-*stilbene by sulphuric acid.* The literature contains no reference to the polymerisation of either *cis*- or *trans*-stilbene by concentrated sulphuric acid. The addition of a drop of concentrated sulphuric acid to about 1 ml. of *cis*-stilbene

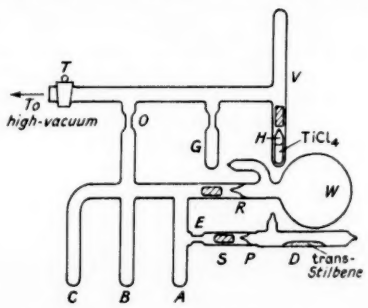
produced a light yellow dispersion, considerable heat evolution, and a great increase in the viscosity of the mixture. From this a colourless, glassy transparent resin was isolated. A similar product was obtained from *trans*-stilbene by an analogous procedure.

2. *Interaction of* cis- *and* trans-*Stilbene with Titanic Chloride* in vacuo.—Preliminary experiments demonstrated that *cis*-stilbene was not isomerised in the presence of Friedel–Crafts catalysts but that, depending on the presence or absence of a suitable co-catalyst, either polymerisation or no reaction at all occurred. As a result of these observations it was decided to investigate the interaction of the stilbenes with titanic chloride under more rigorously defined conditions.

Experimental

Experiment with trans-*Stilbene.—Materials. trans*-Stilbene was prepared by Ballard and Dehn's method (*J. Amer. Chem. Soc.*, **1932**, **54**, 3969) and recrystallised from *n*-hexane to constant m. p. (124°). It was purified by vacuum-sublimation through a series of five phials until it was contained in phial *D* (see Figure). The titanic chloride was a colourless commercial product which was fractionated *in vacuo*, and distilled into phials. One of these (*H*) with a magnetic phial-breaker was sealed into limb *V* of the apparatus.

Apparatus and procedure. When assembled, the whole apparatus was flamed at intervals and evacuated for 24 hours to produce a " black " vacuum ($<10^{-4}$ mm. of Hg). Then tap *T* was closed. Seal *P* was broken and most of the *trans*-stilbene sublimed into *B*, but some was



left in *A*. Constriction *E* was then sealed and vessel *D* removed. With liquid nitrogen round *G*, phial *H* was broken. The first fraction coming off the titanic chloride from *H* was condensed in *G*. Then, with liquid nitrogen round *C*, *G* was sealed and pulled off, the remainder of the titanic chloride from *H* was condensed in *C*, and then *O* was sealed.

Observations. Immediately after the phial *H* was broken, some volatile substance came into contact with the upper portion of the film of *trans*-stilbene in *B* and produced a series of brown bands about 1—1·5 cm. wide. The remainder of the contents of *B* and *A* remained white. However, most of the more volatile portion from the titanic chloride, probably hydrochloric acid, had condensed in *G*. When the titanic chloride had attained room temperature, no change took place in *A* or *B*. By means of liquid nitrogen some of it was distilled into *A* and *B*. As soon as the region where it was in contact with the *trans*-stilbene warmed up, a deep red liquid was formed. Then the titanic chloride was distilled back from *A* and *B* into *C*. The red complex was thereby decomposed and the system reverted to its original condition. Even after the red complex had been thus formed and decomposed six times, the white solid in *A* or *B* could be sublimed, thus proving that no polymerisation had occurred. The brown ring formed in *B* immediately after the breaking of phial *H* could not be sublimed. Therefore this was probably some polymeric material. When cooled in liquid nitrogen the red complex of *trans*-stilbene and titanic chloride became colourless, but the colour returned when it warmed up again. When seal *R* leading to the water-vapour bulb *W* was broken, an immediate brown colour, similar to that produced at the beginning of the experiment at the top of *B*, appeared wherever any white *trans*-stilbene had been present. Since it was impossible to sublime away this brown material, polymerisation must have occurred.

Experiment with cis-*Stilbene.—Apparatus and procedure.* The apparatus was similar to that used for *trans*-stilbene. The main modification was a device for fractionating the titanic chloride after breaking of phial *H*, without letting it come in contact with the *cis*-stilbene.

The *cis*-stilbene, prepared as described previously (Brackman and Plesch, *J.*, 1952, 2188), was distilled once in a high vacuum and sealed off in *D*. After the whole apparatus had been flamed and pumped out for 24 hours, seal *P* was broken, the *cis*-stilbene distilled into *A*, and constriction *E* sealed off. The heat of this operation isomerised some *cis*-stilbene to the *trans*-isomer which adhered as a thin white crystalline film to the wall of *A* near *E*. The phial *H* was then broken, a first small volatile fraction condensed and sealed off in *G*, and the remainder of the titanic chloride put in communication with the three-limbed reaction vessel *A*, *B*, *C* by breaking a glass seal. With the *cis*-stilbene in *A* at room temperature, the titanic chloride was condensed into *C*: only a trace of titanic chloride got into *A*. Finally constriction *O* was sealed.

Observations. As the titanic chloride in *C* warmed to room temperature a deep red colour spread through the *cis*-stilbene in *A*. The film of *trans*-stilbene near *E* remained white. When titanic chloride was condensed on to it the red complex was formed, as in the previous experiment. When *C* was cooled in liquid nitrogen the red *trans*-stilbene complex near *E* was decomposed as before, but the red colour of the contents of *A* did not disappear, except where the *cis*-stilbene was present as a thin film on the wall above the bulk of liquid. By means of this thin layer of *cis*-stilbene it could be shown that the complex formation is reversible. Even after many cycles it showed no sign of isomerisation or polymerisation. When the deep red mixture in *A* was cooled in liquid nitrogen the colour did not change. About an hour after the start of the experiment a very dark red substance with a matt surface had formed in *A*. It could be shown that it contained unpolymerised *cis*-stilbene.

After condensation of the titanic chloride into *A*, water vapour was admitted by breaking seal *R*, and the dark mass in *A* started to bubble, becoming more viscous and leaving colourless shreds of the collapsed bubbles. On warming, the bubbling became more vigorous and a honeycomb structure of semi-solid polymer was formed.

At no time after the admission of the titanic chloride did any evidence appear which indicated that the *trans*-isomer had been produced.

The Structure of the Polymers.—The photo-dimer of stilbene (1 : 2 : 3 : 4-tetraphenyl-*cyclo*butane), m. p. 163°, was prepared as a reference compound by a modification of the method of Pailer and Müller (*Monatsh.*, 1948, **79**, 615). On hydrogenation over platinum in acetic acid this absorbed 1·3 moles of hydrogen per mole of dimer. This indicates that the *cyclo*butane ring is opened by hydrogenation. The infra-red spectrum of the photo-dimer showed that it was absent from the reaction products obtained from *cis*-stilbene (A) and from *trans*-stilbene (B) by the action of sulphuric acid, and from the product (C) obtained in the high-vacuum experiment with *cis*-stilbene.

Product (A) had a molecular weight of 370 (cryoscopic in *cyclo*hexane) [Found: C, 92·8; H, 6·9. $(C_{14}H_{12})_2$ requires *M*, 360; C, 93·3; H, 6·7%]. It absorbed 0·4 mole of hydrogen per mole of dimer. The ultra-violet spectra of (A) and (B) were very similar. They showed peaks near 2650 and 3000 Å. The latter peak was removed by hydrogenation; it indicates the presence of a substance in which a double bond is conjugated with two phenyl groups. Quantitative comparison with the spectrum of *trans*-stilbene itself showed that there was only 5—10% of this conjugated material in the reaction products. A plausible structure for it is 1 : 2 : 3 : 4-tetraphenylbut-1-ene. Comparison of the infra-red spectra of (A) and (B) and of those obtained after their hydrogenation, with each other and with that of polystyrene, indicated that a major constituent of (A) and (B) was probably 3-benzyl-1 : 2-diphenylindane, that (B) contained appreciably more of this than did (A), and that the indane ring was probably opened by our hydrogenation technique. The nature of the unhydrogenatable constituent(s) is still obscure.

Product (C) was a brittle, transparent, pale yellow resin of molecular weight 438. It was therefore probably a mixture of dimers and trimers (Found: C, 93·2; H, 6·7%). The ultra-violet spectra before and after hydrogenation showed that this reaction product also contained a small proportion of double bonds conjugated with benzene rings. These are again ascribed to the but-1-ene and/or the corresponding stilbene trimer. The structure of the main constituents of the mixture is not known, but by analogy with products (A) and (B), and with those obtained in benzene solution by the action of titanic chloride and trichloroacetic acid (Brackman and Plesch, "Cationic Polymerisation and Related Complexes," W. Heffer and Sons, Cambridge, 1953, p. 103), the indane structure seems likely. This would also be analogous to the dimer of 1 : 1-diphenylethylene obtained by Schoepfle

and Ryan (*J. Amer. Chem. Soc.*, 1930, **52**, 4021) by the action of stannic chloride and hydrogen chloride in benzene solution, to which they assigned the structure 3-methyl-1 : 1 : 3-triphenylindane. In the absence of deliberately added hydrogen chloride these workers obtained the 1 : 1 : 3 : 3-tetraphenylbut-1-ene.

Discussion.—The present experiments, in agreement with those of Downing and Wright (*loc. cit.*), show that *cis*-stilbene is not isomerised by the action of boron fluoride or titanic chloride. Price and Meister (*loc. cit.*), who first reported this reaction, do not give any evidence that the solid isolated by them after the interaction of *cis*-stilbene and boron fluoride was indeed *trans*-stilbene; it is quite possible that they mistook a polymer for the *trans*-isomer. Thus, there is now no evidence for the direct interaction of boron fluoride with double bonds, and there is much evidence against it (A. G. Evans and Weinberger, *Nature*, 1947, **159**, 437; A. G. Evans and Meadows, *J. Polymer Sci.*, 1949, **4**, 359; A. G. Evans, *J. Appl. Chem.*, 1951, **1**, 240; *op. cit.*, p. 20; Meier, *loc. cit.*). Any theories based upon such interaction must therefore be revised.

The high-vacuum experiments described above show that *cis*- and *trans*-stilbene react reversibly with titanic chloride, in the absence of a third substance, to give two different complexes. Both complexes are deep red, but the colour of the *trans*-stilbene complex is destroyed reversibly by cooling in liquid nitrogen. The complex from *cis*-stilbene is appreciably more stable than that from the *trans*-isomer. There was no evidence that *cis*-stilbene was isomerised by complex formation. In the presence of a suitable co-catalyst (water, and possibly hydrochloric acid) both isomers formed polymers under the influence of titanic chloride. Thus, during complex formation with titanic chloride the two isomers retain their identity and therefore the hydrocarbon cannot be fully ionised in the complex, as was postulated for the (hypothetical) boron fluoride complex of *cis*-stilbene by Price and Meister (*loc. cit.*). Our results are also in contrast to those of Euler and Willstaedt (*Arkiv Kemi, Mineral., Geol.*, 1929, **10**, *B*, No. 9; *Chem. Abs.*, 1929, **23**, 4465) who found that by reaction in anhydrous chloroform both isomers gave the same complex with antimony trichloride, $(C_6H_5{\cdot}CH{:})_2,2SbCl_3$ (m. p. 106—107°), and with ferric chloride, $(C_6H_5{\cdot}CH{:})_2,2FeCl_3$, which could be heated to 326° without melting. The complexes from both halides were colourless. These two halides have a greater similarity to aluminium chloride than to the Group IV halides and the properties of these complexes, which differ from those of the titanic chloride complexes, may well be further evidence for Plesch's suggestion (*J. Appl. Chem.*, 1951, **1**, 269) that there is a fundamental difference between the mode of action of boron fluoride and the Group IV halides on the one hand, and the other tervalent halides on the other. The present results also add yet another to the list of polymerisations catalysed by metal halides, for which it has been shown that the presence of a co-catalyst is essential.

The structure of the polymers indicates that chain growth probably stops predominantly by an internal Friedel–Crafts reaction. This seems to be a general feature of the cationic polymerisation of arylenes, since polystyrenes and poly-α-methylstyrenes produced in this way also lack unsaturation (Dainton *et al.*, *op. cit.*, p. 80). This is in contrast to cationically produced polyalkenes in which unsaturated end-groups predominate.

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260. *The Mechanism of Carbohydrase Action. Part I. The Preparation and Properties of Maltodextrin Substrates.*

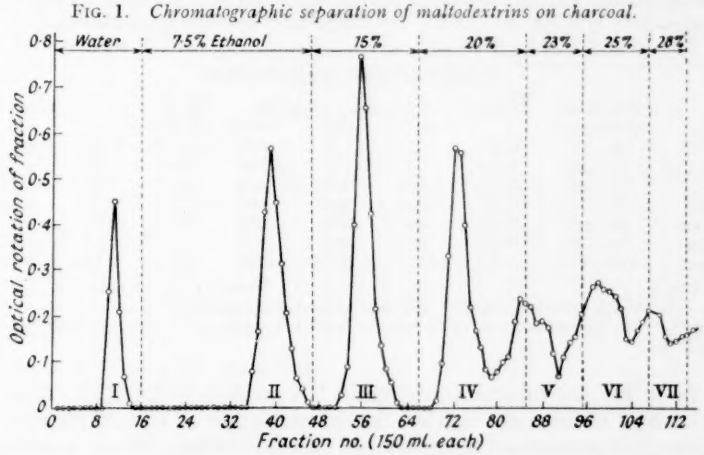
By W. J. Whelan, J. M. Bailey, and (in part) P. J. P. Roberts.

The partial acid hydrolysis of potato amylose, followed by fractionation of the products on a column of charcoal–Celite, leads to the isolation in pure form of a series of linear dextrins of which maltose is the lowest typical member. Certain physical properties of the maltodextrins are described, together with an account of their hydrolysis by β-amylase.

In a preliminary communication (*J.*, 1950, 3692) Bailey, Whelan, and Peat reported the isolation of the lowest members of the series of linear dextrins derived from amylose. The method by which this separation was effected, and some of the properties of the dextrins, are now described in detail.

The basis of the method of fractionation is that described by Whistler and Durso (*J. Amer. Chem. Soc.*, 1950, **72**, 677) who showed that a mixture of mono-, di-, and tri-saccharides can be separated by chromatography on a charcoal–Celite column. Monosaccharides are eluted with water, disaccharides with 5% aqueous ethanol (vol./vol.), and trisaccharides with 15% ethanol. As an example the technique was applied by these authors to the successful resolution of a mixture of glucose, sucrose, and raffinose. It seemed probable that molecules of even greater molecular weight might be resolved by the use of higher alcohol concentrations and if this were so the method would be applicable to the resolution of the dextrins derived by acid hydrolysis from amylose, the linear component of starch. Potato amylose was therefore hydrolysed with sulphuric acid until the degree of apparent conversion into glucose was 32·5%. This particular value was chosen on the basis of a calculation, made by using Kuhn's formula (*Ber.*, 1930, **63**, 1503), which indicated that dextrins containing from three to eight glucose units would be produced at this stage in optimum yield. The amylose hydrolysate was neutralised, absorbed on a charcoal–Celite column, and eluted under suction with water. The apparatus is illustrated in Fig. 5. The optical rotation of each fraction was measured.

Fig. 1. *Chromatographic separation of maltodextrins on charcoal.*



I, Glucose. II, Maltose. III, Maltotriose. IV, Maltotetraose.
V, Maltopentaose. VI, Maltohexaose. VII, Maltoheptaose.

Glucose was the only sugar to be eluted by water. Maltose needed 7·5% ethanol, maltotriose 15% ethanol, and further stepwise increments in the alcohol concentration eluted higher saccharides up to maltoheptaose (Fig. 1). Products of even greater molecular weight were later obtained but have not been examined in detail. An absolute separation of the first three sugars was achieved but some mutal contamination occurred

in the elution of maltotetraose and succeeding sugars. In these cases portions of the eluates were rejected after inspection of the elution curves (Fig. 1 and the Table). The fractionation has since been repeated with larger quantities, *viz.*, 20 g., 24 g., and 50 g., of amylose, with similar results.

With the exception of maltose, all the dextrin fractions were refractionated on an acid-washed charcoal. This treatment achieved a dual purpose; first, the purity was increased by rejection of extreme fractions, and, secondly, the ash present in dextrins eluted from untreated charcoal was largely removed. There still remained, however, an interfering substance of unknown constitution. It was reported earlier (*J.*, 1950, 3692) that hypoiodite oxidation of the dextrins gave erratic results whereas estimates of chain-length based on copper-reducing power were satisfactory. It was subsequently discovered, however, that interference with the Somogyi copper reagent (*J. Biol. Chem.*, 1945, **160**, 61) became manifest when the dextrins were hydrolysed to glucose with acid for the purpose of determining their concentration. The cause remains unexplained but it was avoided when the Somogyi reagent was replaced by that of Shaffer and Hartmann (*J. Biol. Chem.*, 1921, **45**, 377). For this reason the values of optical rotation reported in our earlier communication had to be corrected; the corrected values are given in the Table. The final products are yellowish-white amorphous solids; crystallisation has not been attempted.

Properties of the maltodextrins.

Sugar	Fractions combined *	Yield, g. †	Molecular weight ‡ M_1	M_2	Calc.	$[\alpha]_D^{15}$, in H_2O	R_F values at 15° § *A*	*B*	*C*
Glucose	10—13	0·81	—	—	180	52·6°	0·39	0·45	0·12
Maltose	36—44	0·91	—	—	342	136·0	0·36	0·41	0·050
Maltotriose	54—62	0·76	500	509	504	160·0	0·305	0·38	0·032
Maltotetraose ...	70—76	0·57	665	666	666	177·0	0·25	0·35	0·018
Maltopentaose...	82—90	0·45	832	843	828	180·3	0·20	0·31	0·012
Maltohexaose ...	94—100	0·33	992	1045	990	184·7	0·18	0·27	—
Maltoheptaose...	104—111	0·22	1147	1150	1152	186·4	0·135	0·23	—

* See Fig. 1. † From 11·2 g. of amylose.

‡ M_1, determined colorimetrically; M_2 determined titrimetrically.

§ Solvents: *A*, phenol–water; *B*, pyridine–fusel oil–water (1 : 1 : 1); *C*, butanol–acetic acid–water (4 : 1 : 5).

Properties of the Maltodextrins.—Although the purified dextrins still contained small amounts (<0·5%) of inorganic matter, the determination of various physical properties indicated that the fractionation procedure had effected absolute mutual separation. Thus, after refractionation, each dextrin gave only a single spot on a paper chromatogram. If it is assumed that acidic fragmentation of amylose effects no change in the configuration of the glucosidic linkages in the fragments then the identity of each dextrin can be determined from a knowledge of the number of glucose units it contains. Indication as to chain-length, available from the order in which the dextrins are eluted from the charcoal column, is supported by evidence detailed below.

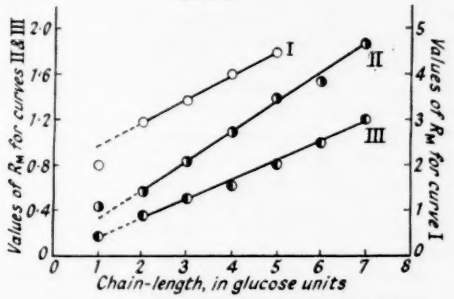
(a) *Paper chromatography.* Paper chromatograms of the maltodextrins obtained with three different solvent systems revealed the expected direct relation between R_M value and molecular weight (Fig. 2) (see Martin, *Biochem. Soc. Symposium* No. 3, 1950, **4**; Bate-Smith and Westall, *Biochem. Biophys. Acta*, 1950, **4**, 428). It is noteworthy that glucose itself does not conform to the relationship exhibited by the maltodextrins. Reference will later be made to this question.

(b) *Molecular weight.* In all quantitative measurements, the concentrations of the dextrin solution were determined by acid hydrolysis and by measurement of liberated glucose (Pirt and Whelan's method, *J. Sci. Food Agric.*, 1951, **2**, 224). The determination of molecular weight by hypoiodite oxidation being unsatisfactory (see above), resort was made to the determination of the copper-reducing power of the dextrin. Two reagents were used, both developed by Somogyi; the first is a colorimetric reagent (*J. Biol. Chem.*, 1952, **195**, 19) requiring 0·2—0·5 mg. of dextrin, and the second is the titrimetric reagent mentioned earlier (*J. Biol. Chem.*, 1945, **160**, 61) which requires 2—3 mg. of dextrin. The times of heating necessary to develop full reducing power were first determined, the time

increasing with the molecular weight of the dextrin. Secondly, these maximal reducing powers were compared on a molar basis with that of maltose, and not with the reducing powers of glucose and maltose (Bailey, Whelan, and Peat, *J.*, 1950, 3692). The colorimetric method yielded, on this basis, values for the molecular weights which were in excellent agreement with the theoretical values (see Table) although agreement was not quite so close with the titrimetric reagent. This relation does not hold if glucose is used as the standard of comparison. For example, with the titrimetric reagent the ratio R_{Cu} for maltose : R_{Cu} for glucose (molar basis) is 1 : 0·927, whereas R_{Cu} for maltose : R_{Cu} for maltotriose is 1. This stresses an important fact sometimes overlooked, namely, that in such a polymeric series of sugars the lowest normal member is not the monosaccharide but the disaccharide, *i.e.*, the smallest molecule containing the glycosidic linkage. It is well known that the copper-reducing power of a sugar is not stoicheiometric with respect to the aldehydic function and is appreciably influenced by the spatial configuration of the hydroxyl groups. Glucose would not, therefore, be expected to conform to the pattern of behaviour of the maltodextrins and should not be regarded as a standard for comparison.

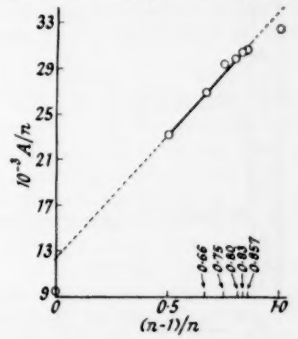
(c) *Optical rotation.* The optical rotations of the sugars (see Table) are plotted in Fig. 3, Freudenberg and Blomquist's relationship (*Ber.*, 1935, **68**, 2070) being used, in which A/n

FIG. 2.



Curve I. Butanol–acetic acid–water.
Curve II. Phenol–water.
Curve III. Pyridine–fusel oil–water.

FIG. 3. *Application of the Freudenberg–Blomquist relationship to the maltodextrins.*

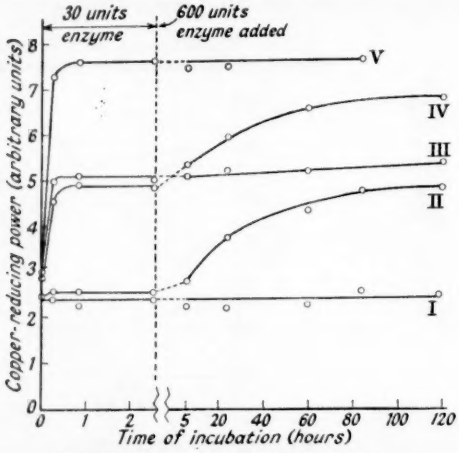


is plotted against $(n-1)/n$, where A is the molecular rotation and n the number of glucose residues per molecule. It will be seen that a linear relationship exists between the values for the maltodextrins but does not hold in the case of the monomer glucose. Whistler and Chen-Chuan Tu (*J. Amer. Chem. Soc.*, 1952, **74**, 3609) have recently reported the isolation, by similar methods, of a series of xylodextrins. It is noteworthy that when we plotted the quoted specific rotations of these xylodextrins, using the co-ordinates of Fig. 3, a linear curve was also obtained and the monomer (xylose) point was not on the curve. The optical rotation of amylose (B.V. 1·41) was found to be $[\alpha]_D$ +201° in aqueous sodium chloride. This value is incorporated in Fig. 3 using $A/n = 32{,}562$ and $(n-1)/n = 1$. It is seen that the amylose point lies below the projection of the straight line joining the maltodextrin points, and the magnitude of the deviation is so great that it must have a real significance. One explanation would be that amylose contains certain structural peculiarities absent from, or less prevalent in, the maltodextrins. It would need to be presumed that these " anomalies " are preferentially removed by the acid treatment in the preparation of the dextrins.

(d) *Action of β-amylase.* Further evidence of the essential purity of the dextrins was obtained from a study of their behaviour towards certain enzymes. The actions of phosphorylase and of α-amylase are reported in forthcoming communications (to be published; Part II, following paper); in the present study the crystalline sweet-potato β-amylase was used. The enzyme was first allowed to act in low concentration on malto-triose, -tetraose, -pentaose, and -hexaose. The results (Fig. 4) show that little hydrolysis of maltotriose took place, but there was rapid hydrolysis of the other three dextrins. The increases in reduc-

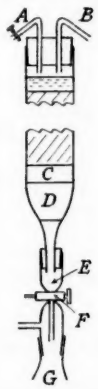
ing power corresponded with the conversion of (i) maltotetraose into two molecular proportions of maltose, (ii) maltopentaose into equimolar proportions of maltose and maltotriose, and (iii) maltohexaose into three molecular proportions of maltose. The enzyme concentration was then increased twentyfold with the result that a slow conversion of maltotriose and more extensive hydrolysis of maltopentaose ensued, occupying several days (Fig. 4). The action of the concentrated enzyme on the previously hydrolysed maltotetraose and -hexaose was slight. The subsequent slow hydrolysis came to an end when maltotriose had been converted into an equimolar mixture of maltose and glucose, and maltopentaose into two molecules of maltose and one of glucose, as determined by reducing power (Fig. 4). It was confirmed by paper chromatography that the deductions as to the nature of these ultimate products of hydrolysis were correct. The maltose fraction eluted from the charcoal column was not attacked by β-amylase. The possibility that the action of the concentrated β-amylase on maltotriose was due to an enzymic impurity cannot be discounted but the lack of action on maltose proves that maltase cannot be that impurity.

FIG. 4. *Action of β-amylase on maltodextrins.*



I, Maltose. IV, Maltopentaose.
II, Maltotriose. V, Maltohexaose.
III, Maltotetraose.

FIG. 5. *Glass column used in charcoal chromatography.*



Dr. Dexter French (personal communication to Professor Peat) reports that a sample of soya-bean β-amylase was without action on maltotriose. It seems possible that a specific maltotriase is involved. It is of interest to compare this observation with that of Roberts and Whelan (*Biochem. J.*, 1952, **51**, xviii) that salivary α-amylase does not attack maltotriose whereas the crystalline enzyme preparation obtained by Meyer *et al.* (*Helv. Chim. Acta*, 1948, **31**, 2158) hydrolysed a sample of our maltotriose (personal communication from the late Professor Kurt Meyer).

The maltodextrins have since been used as substrates in an investigation of the action patterns of α-amylase (Roberts and Whelan, *loc. cit.*) and β-amylase. Their use as primers in amylose synthesis by potato phosphorylase has definitely established that the action of this enzyme is to cause the *simultaneous* apposition of glucose residues (from glucose-1 phosphate) to all primer molecules (Bailey and Whelan, *Biochem. J.*, 1952, **51**, xxiii). In this way the dextrins have been used to prepare linear synthetic polysaccharides, which are homogeneous within narrow limits and of known chain-length. Such synthetic polysaccharides have proved of value in investigations of the mode of action of Q-enzyme (Bailey, Peat, and Whelan, *Biochem. J.*, 1952, **51**, xxiv) and of β-amylase, and also of the relationship of chain-length to iodine stain. Details will be published later. Mould and Synge (forthcoming publication) have used the same synthetic polysaccharides in investigating the fractionation of large molecules.

Experimental

Preparation and Use of Charcoal–Celite Column.—"Activated charcoal for decolorising purposes" (British Drug Houses) was used in the initial fractionations, but for refractionation B.D.H. "Acid-washed charcoal" was preferred for reasons stated earlier. Both brands of charcoal contain an iron compound, probably organic, which contaminates the trisaccharide and higher fractions, being first extracted by the 15% ethanol. Incidentally, this substance is a powerful amylase inhibitor. It may be removed by washing the packed column with an aqueous 0·2M-citrate buffer (pH 7·0) until the yellow iron–citrate complex is completely eluted; about 30 ml. of buffer per 100 g. of charcoal–Celite are required. Celite 535 (Johns-Manville Co., London) is preferred to Hyflo-Supercel since the latter contains appreciable amounts of water-soluble inorganic matter. Equal parts by weight of charcoal and Celite are intimately mixed and washed with distilled water (*ca.* 3 l./100 g. of mixture). The mixture is thoroughly dried at 80° and stored until required. A glass column is used with pads of glass wool (*D*) and cotton wool (*C*) at the bottom (Fig. 5). The mixture is added as a thick slurry in water and is allowed to settle before suction is applied; this precaution is necessary for the speedy elution of the column. The liquid level is never allowed to fall below the level of the charcoal–Celite. When operating the column the concentrated aqueous solution of the mixture to be fractionated is added and suction applied from a water-pump attached to the adapter *E*. When the solution has been absorbed a liquid head is provided by suction through tube *A*, tube *B* being connected to a reservior of eluant. Tube *A* is then closed, and the head of liquid is automatically maintained. Fractions are collected in a graduated receiver (*G*) and when a fraction is removed, air is admitted through the three-way tap (*F*) in order not to interrupt the vacuum applied to the column. Before measurement of the optical rotation, each fraction is clarified by filtration through a modified Seitz filter (H. A. Jones, Beaumaris).

Preparation of Maltodextrins.—Potato amylose (11·2 g.; air-dried; B.V., 1·45; *J.*, 1951, 801) was wetted with ethanol (40 ml.). 6N-Sodium hydroxide (40 ml.) and water (800 ml.) were added with vigorous shaking; the amylose dissolved at room temperature within a few minutes. The solution was neutralised (phenolphthalein) with 6N-sulphuric acid and a further 56 ml. of acid, and water to 1 l. were added, to give a final acid normality of 0·33. The solution was heated in a boiling-water bath, and portions (2 ml.) were removed at intervals for determination of copper-reducing power (as glucose) (Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224). After 80 and 130 minutes the %-conversions (as glucose) were 11·1 and 22·6, respectively. The solution was cooled after 165 minutes and neutralised (phenolphthalein); the conversion was then 32·5%. The original amylose solution was slightly opalescent but during the hydrolysis a precipitate suddenly formed and the supernatant became water-clear. Later examination of this precipitate (*ca.* 500 mg.) suggested that it was a partly degraded amylose. The neutralised solution was concentrated to 200 ml. under diminished pressure at 40°, and was dialysed against distilled water (4 × 1 l.). The combined dialysates were concentrated to 20 ml. and the syrup was added to a charcoal–Celite column (55 × 4·8 cm.) which was irrigated as described above. Fractions of 150 ml. were collected, and the optical rotations measured by using a 4-dm. tube. The eluant was changed as indicated in Fig. 1. At first the column delivered 300 ml. of eluate/hour but the rate gradually decreased to 100 ml./hour. The sugar-containing fractions were combined as shown in the Table and evaporated to dryness under diminished pressure. In later work it was found to be advantageous to redissolve the solid residue by warming it with ethanol and adding water until solution of the sugar was complete; a white powdery residue derived from the adsorbents remained undissolved and was removed by filtration. Refractionation of the dextrins was carried out in the same way and it was usual to reject the first and the last of the fractions which exhibited an appreciable optical rotation. The criterion of purity of the dextrins taken was presence of a single zone on the paper chromatogram. The charcoal column might possibly be used for de-ionising; in the above experiment (see Fig. 1) the sodium sulphate was largely eluted between fractions 6 and 9; glucose was first detected in fraction 10.

Examination of the Dextrins.—(a) *Paper chromatography.* This was carried out at room temperature, the three mixtures of solvents shown in the Table being used. It was usual to employ a spray of benzidine (0·5 g.), dissolved in glacial acetic acid (10 ml.), 40% trichloroacetic acid (10 ml.), and ethanol (80 ml.) to detect the sugar zones.

(b) *Optical rotation.* All quantitative measurements were made on solutions in which the concentration of dextrin was determined by acid hydrolysis to glucose (Pirt and Whelan, *loc. cit.*) and measurement of the reducing power developed. Varying amounts of this reducing

solution were used in the determination, and the relation between reducing power and volume of solution was plotted. With the Somogyi titrimetric reagent (*J. Biol. Chem.*, 1945, **160**, 61) the usual direct relationship was not found but no such interference took place with the Shaffer–Hartmann reagent (*ibid.*, 1921, **45**, 377) which was therefore used in these determinations. In later work it was found possible to remove the interfering substance by the use of the Somogyi deproteinising agents (*ibid.*, 1945, **160**, 69) before the acid hydrolysis. It should be mentioned that the unhydrolysed sugar solution did not exhibit this interference.

(c) *Molecular weight.* Two methods of determination were used. The first utilises the Somogyi copper reagent (*ibid.*, 1952, **195**, 19) and the Nelson arsenomolybdate reagent (*ibid.*, 1944, **153**, 375), as follows. The sugar solution (2 ml.; containing $>0{\cdot}6 \times 10^{-6}$ mole) was placed in a 25-ml. flask and heated in a boiling-water bath with copper reagent (2 ml.). Maltose and maltotriose were heated for 10 minutes and higher dextrins for 25 minutes. After cooling in cold water for 2½ minutes the arsenomolybdate reagent (2 ml.) was added with shaking; after a further minute, water was added to 25 ml. The intensity of colour developed was measured, 5—30 minutes after dilution, against that in a control from which sugar was absent, a Spekker photometer, Ilford 608 filters, and 4-cm. cells being used. With maltose, 0·1 mg. $\equiv 0{\cdot}294 \pm 0{\cdot}003$ (scale reading). The molar concentration, and hence the molecular weight, of a dextrin was obtained by comparing its reducing power with that of maltose. In the second method the Somogyi titrimetric reagent (*loc. cit.*) was used as prescribed by Pirt and Whelan (*loc. cit.*). With maltose a heating time of 20 minutes was necessary for the full development of reducing power. Maltotriose required 30 minutes' heating and 45 minutes was found to be a suitable minimum time for the higher dextrins up to maltoheptaose.

(d) *Action of β-amylase.* Digests were prepared containing approximately equimolar amounts ($2{\cdot}1 \times 10^{-5}$ M) of maltose, malto-triose, -tetraose, -pentaose, and -hexaose; 0·2M-acetate buffer (pH 4·8; 1·5 ml.), crystalline β-amylase (30 units; 0·5 ml.), and water to 11·5 ml. were included. Enzyme activity was determined as in *J.*, 1945, 882. The digests were incubated at 35° and portions (1 ml. each) were withdrawn at intervals up to 2·5 hours for measurement of reducing power, the Somogyi 1945 reagent being used (*loc. cit.*). At this stage a portion (7 ml.) of each digest was removed and mixed with the enzyme (600 units). Incubation was then continued under toluene with further measurements of reducing power as indicated in Fig. 4. The reducing power of the digest components other than the dextrins was determined by using a control digest from which sugar was absent.

The authors are grateful for the advice and encouragement given by Professor Stanley Peat, F.R.S. They wish to thank Professor A. K. Balls, for the gift of crystalline sweet-potato β-amylase, and the Department of Scientific and Industrial Research, for the award of maintenance grants (to J. M. B. and P. J. P. R.).

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR. [*Received, September 24th*, 1952.]

261. *The Mechanism of Carbohydrase Action. Part II.* α-Amylolysis of Linear Substrates.*

By W. J. WHELAN and P. J. P. ROBERTS.

The end-products of the action of purified salivary α-amylase on amylose and the maltodextrins derived from it have been examined. Only two end-products are found, namely, maltose and maltotriose. This examination supports the theory of α-amylase action first advanced by Meyer and Bernfeld, which states that in an amylose-type chain, α-amylase can hydrolyse any except the two terminal α-1 : 4-linkages. The ratios of maltose to maltotriose which are produced by α-amylolysis of these substrates are found to be in exact agreement with values obtained by calculation on the basis of Meyer's theory. It is also demonstrated that the susceptible linkages in a given substrate molecule are all hydrolysed by α-amylase at the same rate.

THE present investigation of the action of a purified amylase on the separated components of starch had the purpose of gaining an insight into the mechanism of α-amylolysis by examination and characterisation of the end-products.

Human saliva was chosen as the source of the enzyme, and the purification method of

* Part I, preceding paper.

Meyer, Fischer, Staub, and Bernfeld (*Helv. Chim. Acta*, 1948, **31**, 2158) was used, the enzyme being purified to the stage before crystallisation. A preliminary account of the present work, which is concerned with the amylose component of starch, has already been given (Roberts and Whelan, *Biochem. J.*, 1951, **49**, lvi; 1952, **51**, xviii). Studies on amylopectin and glycogen have been reported elsewhere (Whelan and Roberts, *Nature*, 1952, **170**, 748). In Fig. 1 is demonstrated the action of salivary α-amylase (referred to subsequently as α-amylase) on potato amylose as measured by the development of reducing power. The reaction was of the first order and ceased abruptly at an apparent conversion into maltose of 90·8%. At this stage the enzyme was still active and no further reaction occurred when fresh enzyme was added. In large-scale experiments, considerable difficulty was experienced because of the precipitation of amylose when the enzyme was added. This effect was largely eliminated by the addition of sodium chloride to the digest.

After the attainment of the limiting conversion, a digest of amylose (3·023 g.) was heated to deactivate the enzyme, concentrated, and a portion of the products, equivalent to 2·708 g. of amylose, was fractionated on a charcoal–Celite column as described by Bailey, Roberts, and Whelan (preceding paper). The progress of the fractionation is recorded in Fig. 2. Perfusion of the column with water yielded no monosaccharide fraction although the method of determining the sugars, namely by measurement of optical rotation, was sufficiently sensitive to detect 10 mg. of glucose. Elution of the column with 7·5% ethanol

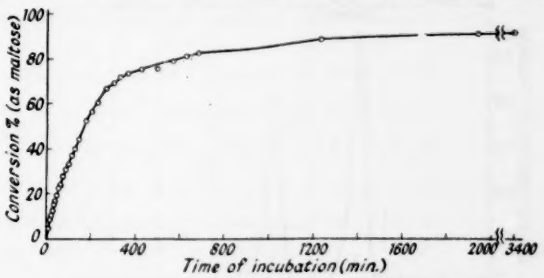


FIG. 1. *α-Amylolysis of potato amylose at* pH 7·0.

extracted maltose, identified by its β-octa-acetate, and 15% ethanol eluted maltotriose, identified as its β-undeca-acetate (Table 1) and by hydrolysis with β-amylase (Table 3). The products were also compared with authentic samples. These sugars were apparently the sole products since elution with higher concentrations of alcohol yielded no other substance (Fig. 2). The combined yield of maltose and maltotriose was equivalent

TABLE 1. *Properties of α-Limit Dextrins from Amylose.*

	Yield,			β-Acetate,*†				
Sugar	g.	10^{-3} mole	$[\alpha]_D$, in H_2O	m. p.	$[\alpha]_D$, in $CHCl_3$	R_F ‡ value	Reduction § equiv.
Maltose (anhydrous)	1·623	4·745	(*a*) 136°	159—160°	+63°	0·41	0·235
			(*b*) 136	159—160	+62·6	0·41	0·230
Maltotriose	0·999	1·983	(*a*) 160	134—136	+86	0·38	0·346
			(*b*) 160	135—137	+85	0·38	0·343

* From 2·708 g. of amylose.
† See Wolfrom *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2874.
‡ In pyridine–fusel oil–water (1 : 1 : 1).
§ Expressed as mg. of sugar/ml. of 0·005N-thiosulphate, the Somogyi copper reagent being used (*J. Biol. Chem.*, 1945, **160**, 61).
(*a*) Values for authentic specimens; (*b*) experimental values.

to 92·4% of the amylose hydrolysed. Elution of maltose and higher saccharides from a charcoal column is not, however, quantitative (see later), but the losses of maltose and maltotriose are almost the same. When the two sugars are mixed in the proportion found in the above experiment, the mixture has a reducing power equivalent to 88·9% of apparent maltose. The reducing power observed at the end of the reaction was 90·0% of maltose.

The fact that the only detectable products of α-amylolysis of potato amylose are maltose and maltotriose may be held to conflict with the demonstration of the presence of β-linkages in potato amylose by Peat, Thomas, and Whelan (*J.*, 1952, 722). The presence of these

linkages is made manifest by the incompleteness (*ca.* 70%) of the β-amylolysis of amylose but inasmuch as one such linkage per amylose chain would suffice to account for the fact that β-amylolysis is incomplete and as the molecule of potato amylose contains about 1000 glucose residues (Potter and Hassid, *J. Amer. Chem. Soc.*, 1948, **70**, 3488) the yield of, for example, a disaccharide containing the β-linkage need not be greater than 0·2% of the weight of amylose used.

The problem now arises of interpreting the action of α-amylase in terms of its products. Whilst this work was in progress, Meyer and Gonon (*Helv. Chim. Acta*, 1951, **34**, 294) reported a study of the action of two α-amylases on amylose in which it was shown, by differential fermentation with yeast, that glucose, maltose, and unfermentable material were produced. The last-named substance (presumed to be maltotriose) was slowly hydrolysed by the α-amylases, yielding glucose and maltose; the reaction was not, however, carried to completion. Glucose and maltose were therefore stated to be the ultimate end-products. These results were deemed to support the hypothesis advanced by Meyer and Bernfeld (*Helv. Chim. Acta*, 1941, **24**, 359E) to the effect that α-amylase acts in a random fashion on all the α-1 : 4-links in an amylose-type chain except only such as are terminal linkages. If this is the course of events then amylose must of necessity give rise to maltose and maltotriose as end-products since both sugars contain only terminal linkages. Meyer

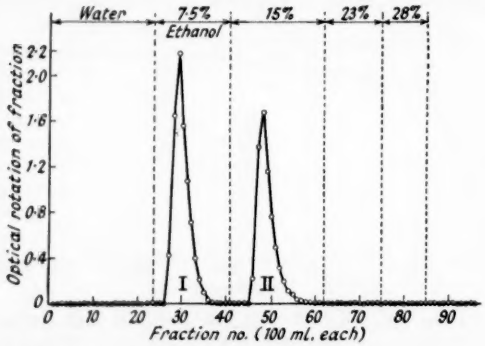


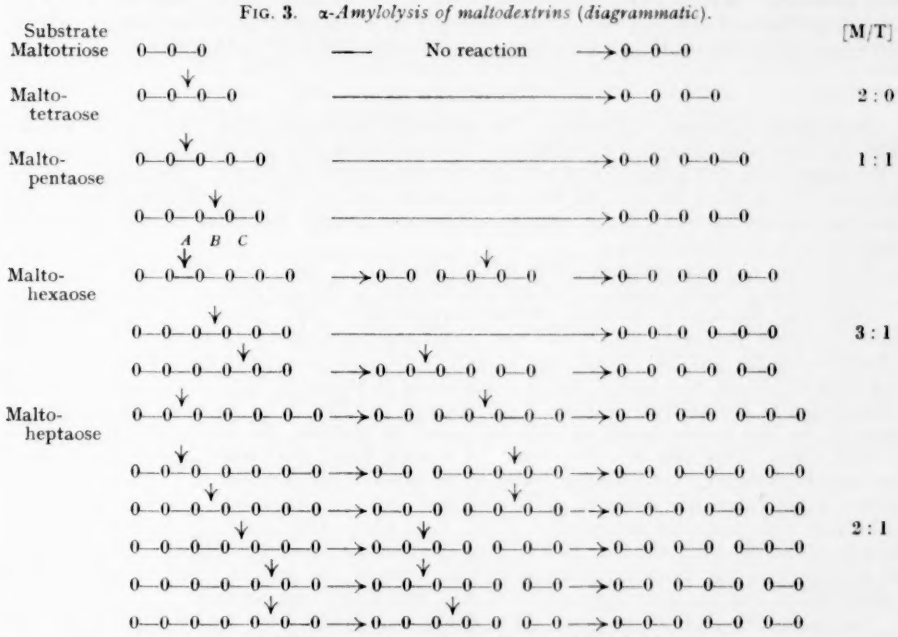
FIG. 2. *Charcoal fractionation of amylose α-limit dextrins.*
I, Maltose. II, Maltotriose.

and Gonon's results would appear to be the same as those reported by us except that the crystalline enzymes used by the Swiss authors seem to effect the further hydrolysis of maltotriose to maltose and glucose. This observation is obviously at variance with the proposed theory of α-amylase action if the crystalline α-amylases are to be regarded as enzymically pure. Our amorphous preparation of salivary amylase has been repeatedly tested for action on maltotriose but no evidence of hydrolysis has been observed (Table 3). Descloux, quoted by Meyer and Gonon (*loc. cit.*), has been able, by a mathematical treatment of α-amylase action, to calculate the maltose : glucose ratio at the end of the reaction for amylose-type chains of any length. On the same mathematical basis we have calculated the relative amounts of maltose to maltotriose which result when the latter is not further hydrolysed. In the case of amylose the calculation leads to a molar ratio of maltose : maltotriose of 2·35 : 1. The molar ratio found by experiment was 2·39 : 1 (Table 1), in excellent agreement with the calculated value.

Further evidence in support of Meyer's conception of α-amylase action comes from an examination of the yields of maltose and maltotriose produced by α-amylolysis of the maltodextrins, the linear dextrins of low molecular weight isolated from acid-hydrolysed amylose as described in the preceding paper. Since the calculated ratios of maltose : maltotriose for the dextrins differ widely, it is possible to subject the above hypothesis to a rigorous test. These ratios may be calculated by the method quoted above or obtained by inspection. The inspection method is illustrated in Fig. 3 for the series of dextrins from maltotriose to maltoheptaose and consists in the consideration of all possible ways in which the dextrin may be hydrolysed and summation of the amounts of maltose and maltotriose which would result.

In studying the α-amylolysis of the maltodextrins about 30 mg. of each dextrin were used. The dextrin was hydrolysed to completion by the enzyme and a portion of the digest was fractionated on a small charcoal–Celite column. The recoveries of maltose and

FIG. 3. *α-Amylolysis of maltodextrins (diagrammatic).*



* [M/T] = molar ratio [maltose : maltotriose].

maltotriose from an artificial mixture (28 mg.) were 94·4 and 95·2%, respectively. Maltotriose, as mentioned earlier, was not attacked by the α-amylase, maltotetraose gave only maltose, while malto-pentaose, -hexaose, and -heptaose were each degraded to mixtures of maltose and maltotriose. The corrected yields of maltose and maltotriose, expressed as molar ratios, are shown in Table 2, and are compared with the calculated ratios. The observed reducing powers of the digests after α-amylolysis are also compared with predicted values for the particular mixture of maltose and maltotriose. In every case the results confirm the validity of the hypothesis.

TABLE 2. *α-Amylolysis of maltodextrins; maltose and maltotriose ratios.*

	Calc. values		Exptl. values	
Maltodextrin	% Conversion (as maltose)	[M/T] *	% Conversion (as maltose)	[M/T] *
Maltotriose	0·0	—	0·0	—
Maltotetraose	100·0	2·00 : 0	99·4	2·00 : 0
Maltopentaose	80·0	1·00 : 1	79·4	1·00 : 1
Maltohexaose	88·8	3·00 : 1	86·1	2·98 : 1
Maltoheptaose	85·7	2·00 : 1	84·6	2·00 : 1

* [M/T] = molar ratio [maltose : maltotriose].

It should be noted that the assumption is implicit in all these calculations that in a given substrate each link which may be attacked by α-amylase is hydrolysed at the same rate. The demonstration, by the above method, of the mode of action of α-amylase provides at the same time evidence which justifies this assumption. Our argument may be illustrated by the case of maltohexaose. α-Amylase can hydrolyse the three linkages, marked *A*, *B*, and *C* in Fig. 3. If *B*, being the most remote from the chain ends, is more easily hydrolysed than *A* or *C*, as is postulated by Myrbäck and Sillen (*Svensk Kem. Tid.*, 1944, **56**, 60), then the ratio maltose : maltotriose should be less than 3 : 1, since hydrolysis

of link *B* gives rise only to maltotriose, which is not futher hydrolysable. These experiments shed no light on the question as to whether the rate of hydrolysis of a linkage is the same in substrates of different molecular size and this question is being examined by other methods. Myrbäck and Magnusson (*Arkiv Kemi, Mineral., Geol.*, 1945, **20**, *A*, No. 14) claim that the end linkages (which are resistant to α-amylase) are more readily split by acid than are the internal links, all of which are presumed to be hydrolysed at the same rate.

Experimental

Preparation of Salivary α-Amylase.—The method of Meyer *et al.* (*Helv. Chim. Acta*, 1948, **31**, 2158) was used with the following variation. Human saliva (750 ml.) was purified as described to the stage of the first precipitation with ammonium sulphate at pH 8·0. The precipitate was then dissolved in water (40 ml.) and 0·2M-citrate buffer (pH 7·0; 20 ml.) and freeze-dried. The resulting preparation was a white, slightly hygroscopic powder, stable for an indefinite period when stored in the refrigerator.

Preparation of Potato Amylose.—The method given in *J.*, 1951, 801, was used.

Preparation of Maltodextrins.—The method recorded in the preceding paper was used.

Small-scale Digestion of Amylose.—Potato amylose (B.V., 1·41; 115·2 mg.) was dissolved in hot 0·1N-sodium hydroxide, the solution was cooled and neutralised with 1N-sulphuric acid, and 0·2M-citrate buffer (pH 7·0; 10 ml.) was added. α-Amylase solution (1 mg.; 1 ml.) and water to a total of 100 ml. were added, and the digest was incubated at 35°. An immediate partial precipitation of the amylose occurred. At intervals portions (5 ml. each) of the digest were removed for the measurement of reducing power as maltose, the Somogyi copper reagent (*J. Biol. Chem.*, 1945, **160**, 61) being used. A control digest from which amylose was absent was used to determine the reducing power of the other digest components. After 24 hours a portion of the digest was removed and centrifuged, and the supernatant solution (10 ml.) was hydrolysed with acid (Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224) in order to determine the polysaccharide concentration; 22·2% of the amylose had been precipitated. After allowance for precipitation the measured reducing powers after 20, 24, and 44 hours corresponded to conversions of amylose into maltose of 91·0, 90·0, and 91·0%, respectively.

Large-scale Digestion of Amylose.—In a similar experiment with 3 g. of amylose in a 1-l. digest, an almost complete precipitation of the amylose occurred on the addition of enzyme. Since a chance observation had indicated that the extent of precipitation was lessened in the presence of sodium chloride the effect of various salts in preventing precipitation was investigated. Amylose (100 mg.; air-dried) was heated in boiling water for 10 minutes and undissolved material was removed. The amylose concentration was determined by acid hydrolysis to glucose (as above). The clear supernatant solution was incorporated in digests of the following composition: amylose solution (7 ml.), 0·2M-citrate buffer (pH 7·0; 1 ml.), enzyme solution (1 ml.), and 1M-salt solution (1 ml.), each digest being contained in a 15-ml. centrifuge tube. The following salts were used: sodium chloride, sodium sulphate, disodium hydrogen phosphate, magnesium chloride, magnesium sulphate, and (0·667M) aluminium sulphate. Two additonal digests were prepared; in one, water replaced salt solution (digest *A*) and in the other water replaced enzyme and salt solutions (digest *B*). All digests were incubated at 35° and after 7 hours each digest was centrifuged and an aliquot (8 ml.) removed. Acid hydrolysis, as above, was used to determine the concentration of polysaccharide remaining in solution. The following results refer to the percentage of the amylose which had precipitated from solution in each case: digest *A*, 9·5%; digest *B*, 0%; NaCl, 1·3%; Na_2SO_4, 10·0%; Na_2HPO_4, 5·3%; $MgCl_2$, 36%; $MgSO_4$, 39%; $Al_2(SO_4)_3$, 19%. Sodium chloride was thus shown to be effective in preventing precipitation. A further difficulty encountered was that this salt was ineffective when the amylose had been dried *in vacuo* at 60°. Air-dried amylose containing about 20—30% of volatile matter was therefore used. This is the concentration found in amylose prepared as in *J.*, 1951, 801. A digest containing air-dried amylose (443·8 mg. ≡ 294·7 mg. dry wt.), α-amylase (2 mg.), 0·2M-citrate buffer (pH 7·0; 12 ml.), 1N-sodium chloride (12 ml.), and water to 100 ml. was incubated at 35°. Hydrochloric acid, instead of sulphuric acid, was employed to neutralise the alkali used in dissolving the amylose. By using the methods given above, the apparent degree of conversion of the amylose into maltose and the extent of precipitation were determined. The results of the experiment, in which the precipitation (6·4%) has been allowed for, are given in Fig. 1.

A similar experiment on a ten-fold scale was carried out. The digest (1 l.) contained amylose (B.V. 1·47; 4·5533 g. wet wt., 3·023 g. dry wt.), 0·2M-citrate buffer (pH 7·0; 100 ml.), 1N-

sodium chloride (120 ml.), and freeze-dried α-amylase (20·8 mg.). After incubation for 24 hours at 35° the polysaccharide concentration was found by acid hydrolysis to be equivalent to 2·827 g. of amylose/l. Consequently, 0·196 g. or 6·5% of the amylose had been precipitated on addition of the enzyme. At this stage the measured reducing power of the digest corresponded to an apparent conversion into maltose of 87·4%. After 32 hours the conversion was 90·0% and the same value was found after 69 hours, a qualitative test then showing the enzyme to be still active. The digest was then heated in a boiling-water bath for 5 minutes in order to deactivate the enzyme. After cooling, 958 ml. of the digest (≡ 2·708 g. of amylose) were transferred to a distillation flask and concentrated to dryness under diminished pressure.

Fractionation of α-Dextrins.—The methods and apparatus used in charcoal chromatography are described in Part I (preceding paper); a column (3 × 45 cm.) of charcoal–Celite 535, prepared and treated as previously described, was used. The amylose α-dextrins were dissolved in a small volume of water and transferred to the column which was then irrigated successively with water, 7·5%, 15%, 23%, and 28% aqueous ethanol, as indicated in Fig. 2. Fractions (100 ml. each) were collected and filtered through a Seitz filter, and the optical rotation measured in a 4-dm. tube. For the recovery of the disaccharide, fractions 26—38 were combined and taken to dryness under diminished pressure. Similarly, the trisaccharide was obtained from combined fractions 45—58. The solids were each dissolved in water, and the solutions transferred to 500-ml. flasks and diluted to the mark. The concentration of each sugar was determined by acid hydrolysis, the optical rotations were measured, and the specific rotations calculated (Table 1). The reducing power of each sugar was compared with that of a corresponding authentic specimen. The mobility of each sugar on paper in the solvent system fusel oil–pyridine–water was similarly compared (Table 1). The sugar solutions remaining were then taken to dryness under diminished pressure.

Acetylation of the α-Limit Dextrins.—The maltose (290 mg.) was heated at 120—130° with anhydrous sodium acetate (240 mg.) and acetic anhydride (3·2 ml.) until the solid had dissolved. The cooled solution was poured into ice–water, and the precipitated acetate (487 mg., 87%) was crystallised from ethanol (see Table 1). The maltotriose (389·9 mg.) was similarly treated but the solid obtained could not be satisfactorily crystallised, showing a tendency to revert to a syrup on exposure to air. Its optical rotation (+88·5°) was somewhat higher than that reported for maltotriose β-undeca-acetate, namely +86° (Wolfrom, Georges, Thompson, and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 2875). These workers had isolated the acetate by chromatogaphy on Magnesol–Celite, and we resorted to this method of purification. Maltotriose (106·3 mg.) was acetylated and the resulting solid (148·3 mg., 79%) was dissolved in benzene (5 ml.) and placed on a column (25 × 3 cm.) of Magnesol–Celite (5 : 1). The column was eluted under suction with benzene–ethanol (100 : 1, vol./vol.) and 100-ml. fractions were collected, the optical rotation of each being determined. Fractions 7—11 were combined and evaporated to dryness under reduced pressure; the resulting solid (69·4 mg.) was crystallised without difficulty from ethanol and its properties determined (see Table 1).

α-Amylolysis of Maltodextrins.—In a control experiment maltose monohydrate (17·58 mg.) and maltotriose (10·44 mg.) were mixed and fractionated on charcoal–Celite (24 × 1·5 cm.), following the procedure outlined in the preceding paper. The optical rotation of each fraction (20 ml.) was measured in a 2 dm. tube. After elution with water (200 ml.), maltose was removed with 7·5% ethanol (140 ml.), and maltotriose with 15% ethanol (140 ml.). The sum of the rotations due to maltose was 0·430° and for maltotriose was 0·318°. These values corresponded to recoveries of 94·4% and 95·2%, respectively. In the experiments to be described the yields of maltose and maltotriose were corrected for this measured loss of sugar. The method has the advantage of avoiding any error due to the effect of alcohol on the optical rotation of the sugar. In a typical digestion of a maltodextrin, maltohexaose (32·1 mg.) was treated with α-amylase (1 mg.) at 35° in a 25-ml. digest containing 0·2M-citrate buffer (pH 7·0; 3 ml.). Portions (1 ml. each) were removed at intervals for determination of reducing power. After 37 hours the degree of apparent conversion into maltose was 85·4% and after 61 hours was 86·1%. At this stage a portion of the digest (13·58 ml.) was removed and fractionated on charcoal–Celite as described above. The corrected sum of the rotations due to maltose was 0·333°, and for maltotriose, 0·194°. These values correspond to molar quantities of $3{\cdot}58 \times 10^{-5}$ and $1{\cdot}20 \times 10^{-5}$, respectively, and a molar ratio of 2·98 : 1 (see Table 2). The yield of maltose (anhydrous) was also determined by measurement of reducing power and found to be 11·47 mg.; the actual yield as determined by optical rotation was 11·54 mg.

Action of α- and β-Amylase on Maltotriose.—Maltotriose (25 mg.), α-amylase (2 mg.), and 0·2M-citrate buffer (pH 7·0; 3 ml.) were mixed, diluted to 25 ml., and incubated at 35°. At

intervals, portions (2 ml.) were removed and the reducing power measured by using the Somogyi reagent (*loc. cit.*). In Table 3 these reducing powers are expressed in terms of 0·005N-sodium thiosulphate solution. Similar digests were prepared containing crystalline sweet-potato β-amylase (*ca.* 1000 units; see *J.*, 1945, 882) or purified soya-bean β-amylase (*ca.* 1000 units; *J.*, 1952, 714) instead of α-amylase and were incubated at pH 4·8 and 35°. In these cases a slow but complete conversion of maltotriose into equimolar amounts of maltose and glucose took place (see Table 3).

TABLE 3. *Action of α- and β-amylase on maltotriose.*

Enzyme	Period of incubation (hours)					
	0	22·5	72·8	120	167·5	
Salivary α-amylase	5·46	5·33	5·29	5·36	5·28	ml. of 0·005N-thiosulphate
Sweet-potato β-amylase	0	47·6	87·7	98·9	101	% conversion
Soya-bean β-amylase ...	0	39·9	79·0	96·8	101	% conversion

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262. *Alternative Reaction Patterns in Autosynthetic Systems.*

By SIR CYRIL N. HINSHELWOOD.

Systems of components with enzymic character in which each part depends for its increase upon the operation of another part may in the steady state obey the law of exponential growth as though each separate part were autosynthetic in its own right. In continuation of a previous study (*J.*, 1952, 745) it is shown that this result also holds good if there are alternative ways in which the mutual interdependences operate (alternative reaction patterns). In such cases both patterns may operate simultaneously, or one may show a lag in attaining its steady state while the other is fully operative. If there is competition for some intermediate substance by two competing reaction patterns, the lag of one may be indefinitely prolonged, or only terminated by special circumstances. There may then be fluctuations in growth rate before the steady condition is reached.

The analogy between these effects and some characteristic phenomena observed in the growth of unicellular organisms is pointed out, for example, the persistence of less efficient growth mechanisms in conditions where they can be, and ultimately are, superseded by more efficient ones.

LIVING cells, such as bacteria, capable of independent growth and reproduction contain a considerable number of enzyme systems responsible for very varied reactions of synthesis and degradation. These reactions are co-ordinated and interdependent and can be used in different orders and combinations to give the final duplication of the cell material. A particular combination of the partial reactions associated with definite proportions of the enzymic components and definite velocity constants may be termed a reaction pattern of the cell. In view of the widely different substrates which a bacterial cell can utilise and the great number of individual steps in the synthesis or breakdown of its substance, there must be alternative sequences in which the individual steps of oxidation, reduction, hydrolysis, condensation, deamination, transamination, and so on are arrangeable, and these constitute alternative reaction patterns. Sometimes the alternatives will be in competition, and it is the purpose of this paper to examine some of the consequences.

The basic assumptions are those of a previous paper (*J.*, 1952, 745), namely, that autosynthesis of the whole cell system occurs not by the self-replication of individual units, but by the co-ordinated action of components whose mutual dependence is expressed by equations of the type :

$$dX_1/dt = \alpha X_2,\ dX_2/dt = \beta X_3,\ dX_3/dt = \gamma X_4,\ dX_4/dt = \delta X_1$$

In such a system the proportion of the constituents varies at first irregularly, but in a final steady state so that each conforms to a simple autocatalytic equation $X_n = (X_n)_0 e^{kt}$.

The mode of interdependence represented by the above equations is indeed that thought to be shown by proteins and nucleic acids in cells (Malmgren and Heden, *Acta Path. Microbiol. Scand.*, **1947**, **24**, 448; Caldwell and Hinshelwood, *J.*, **1950**, 3156), each of which directs the formation of the other.

In the previous paper the model employed was that of a single sequence of changes, and the consequences indicated the possibility of adaptive phenomena, reversible in principle but in appropriate conditions very much delayed. The general correspondence of the predicted phenomena with observations on the growth and training of bacteria was pointed out. The problem now is to schematise in a simple way the existence of the alternative networks just referred to. The following assumption will therefore be made. A given component present in total amount R in the whole system (irrespective of the number of cells) gives rise by interaction with one substrate or intermediate to an enzyme represented in amount by X_1 and with another substrate or intermediate to a different enzyme represented by Y_1. Thus

$$\mathrm{d}X_1/\mathrm{d}t = \alpha R \quad \text{and} \quad \mathrm{d}Y_1/\mathrm{d}t = aR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

X_1 and Y_1 in their turn condition the formation of X_2 and Y_2 respectively according to the equations :

$$\mathrm{d}X_2/\mathrm{d}t = \beta X_1 \quad \text{and} \quad \mathrm{d}Y_2/\mathrm{d}t = bY_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In order that the mutual dependences shall form a closed cycle and so typify the essential organisation of a cell, as in the earlier discussion, R must be formed under the influence of X_2 or Y_2 or both :

$$\mathrm{d}R/\mathrm{d}t = \gamma X_2 + cY_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Thus schematically the system $R \longrightarrow X_1 \longrightarrow X_2$ of the earlier treatment has now been elaborated to $Y_2 \longleftarrow Y_1 \longleftarrow R \longrightarrow X_1 \longrightarrow X_2$. For comparison it is also convenient to consider at the same time the simpler branched system $Y_1 \longleftarrow R \longrightarrow X_1$, which will be represented by the equations :

$$\mathrm{d}X_1/\mathrm{d}t = \alpha R, \ \mathrm{d}Y_1/\mathrm{d}t = aR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\mathrm{d}R/\mathrm{d}t = \beta X_1 + bY_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The meaning of (1) and (4) can be further developed as follows. In certain suitably supplied media there will occur substrates and intermediates such that α and a are both finite. One compound is guided by R (*e.g.*, by a nucleic acid structure) into the building up of an enzyme X_1, while another, probably not differing too much from the first in character, is guided by the same structure R into the building up of a different enzyme Y_1. In some other medium the available materials may be such that either α or a is permanently equal to zero. α and a thus determine alternative and on occasion competing reaction paths. X_1 and Y_1 according to this view would represent structurally related enzymes, or, perhaps better, structural modifications of a given enzyme system arising from modified substrates under the influence of a single formative agency.

Steady Ratios and Exponential Growth.—The solutions of (4) and (5) are found by standard methods and are :

$$R = \tfrac{1}{2}\left\{R_0 + \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}\mathrm{e}^{kt} + \tfrac{1}{2}\left\{R_0 - \frac{\beta(X_1)_0 + b(Y_1)_0}{k}\right\}\mathrm{e}^{-kt} \quad . \quad . \quad . \quad (6a)$$

$$X_1 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} =$$

$$\tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} + \frac{\alpha}{k}R_0\right\}\mathrm{e}^{kt} + \tfrac{1}{2}\left\{(X_1)_0 + \frac{\alpha b(Y_1)_0 - ab(X_1)_0}{k^2} - \frac{\alpha}{k}R_0\right\}\mathrm{e}^{-kt} \quad . \quad (6b)$$

$$Y_1 = (a/\alpha)\{X_1 - (X_1)_0\} + (Y_1)_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6c)$$

where $k^2 = \alpha\beta + ab$.

When growth has been long continued under constant conditions, steady ratios of R, X_1, and Y_1 are established, and each of these quantities follows the simple exponential law during its subsequent increase. The steady ratios are $X_1/R = \alpha/k$, and $Y_1/R = a/(\alpha\beta + ab)^{\frac{1}{2}} = a/k$. If a small portion of the system is isolated and transferred to a

fresh supply of medium, as in the subculture of bacteria, R_0, $(X_1)_0$, and $(Y_1)_0$ are now in the ratio $\alpha : a : k$ so that equations (6*a*), (6*b*), and (6*c*) become respectively $R = R_0e^{kt}$, $X_1 = (X_1)_0e^{kt}$, and $Y_1 = (Y_1)_0e^{kt}$.

It has been shown that the length of the chain of interdependent processes does not affect the conformity with the simple law, and it now appears that, in principle, bifurcations in the chain also do not.

The same result holds good for the rather more complex example described by equations (1), (2), and (3). The solutions are as follows

$$R = A_1e^{kt} + B_1e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_1e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad (7a)$$

$$X_1 + D_2/k^3 = A_2e^{kt} + B_2e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_2e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad (7b)$$

$$Y_1 + D_3/k^3 = A_3e^{kt} + B_3e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_3e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt \quad . \quad . \quad . \quad . \quad . \quad (7c)$$

$$X_2 + E_4/k^3 = A_4e^{kt} + B_4e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_4e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - D_4t/k^3 \quad . \quad . \quad . \quad (7d)$$

$$Y_2 + E_5/k^3 = A_5e^{kt} + B_5e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt + C_5e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - D_5t/k^3 \quad . \quad . \quad . \quad (7e)$$

where $$k^3 = \alpha\beta\gamma + abc.$$

and

$$A_1 = \frac{1}{3}\left\{R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{c}{k}(Y_2)_0 + \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_1 = \frac{1}{\sqrt{3}}\left\{-\frac{bc(Y_1)_0}{k^2} - \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{c}{k}(Y_2)_0 + \frac{\gamma}{k}(X_2)_0\right\}$$

$$C_1 = \frac{1}{3}\left\{2R_0 - \frac{bc}{k^2}(Y_1)_0 - \frac{\beta\gamma}{k^2}(X_1)_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$A_2 = \frac{\alpha}{k}A_1,\ A_3 = \frac{a}{k}A_1,\ A_4 = \frac{\alpha\beta}{k^2}A_1,\ A_5 = \frac{ab}{k^2}A_1$$

$$B_2 = \frac{1}{\sqrt{3}}\frac{\alpha}{k}\left\{R_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_3 = \frac{1}{\sqrt{3}}\frac{a}{k}\left\{R_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$B_4 = \frac{\alpha\beta}{\sqrt{3}k^2}\left\{-R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0\right\}$$

$$B_5 = \frac{ab}{\sqrt{3}k^2}\left\{-R_0 + \frac{bc}{k^2}(Y_1)_0 + \frac{\beta\gamma}{k^2}(X_1)_0\right\}$$

$$C_2 = \frac{1}{3}\frac{\alpha}{k}\left\{-R_0 + \frac{2bc}{k^2}(Y_1)_0 + \frac{2\beta\gamma}{k^2}(X_1)_0 - \frac{c}{k}(Y_2)_0 - \frac{\gamma}{k}(X_2)_0\right\}$$

$$C_3 = \frac{a}{\alpha}C_2$$

$$C_4 = \frac{1}{3}\frac{\alpha\beta}{k^2}\left\{-R_0 - \frac{bc}{k^2}(Y_1)_0 - \frac{\beta\gamma}{k^2}(X_1)_0 + \frac{2c}{k}(Y_2)_0 + \frac{2\gamma}{k}(X_2)_0\right\}$$

$$C_5 = \frac{ab}{\alpha\beta}C_4$$

$$D_2 = -abc\left\{(X_1)_0 - \frac{\alpha}{a}(Y_1)_0\right\}$$

$$D_3 = -\alpha\beta\gamma\left\{(Y_1)_0 - \frac{a}{\alpha}(X_1)_0\right\}$$

$$D_4 = -\beta abc\left\{(X_1)_0 - \frac{\alpha}{a}(Y_1)_0\right\}$$

$$D_5 = -b\alpha\beta\gamma\left\{(Y_1)_0 - \frac{a}{\alpha}(X_1)_0\right\}$$

$$E_4 = -abc\left\{(X_2)_0 - \frac{\alpha\beta}{ab}(Y_2)_0\right\}$$

$$E_5 = -\alpha\beta\gamma\left\{(Y_2)_0 - \frac{ab}{\alpha\beta}(X_2)_0\right\}$$

The subscript zero indicates the value when $t = 0$. The above solutions can be verified by substitution into equations (1), (2), and (3), and they give the correct values for zero time. When t becomes great enough the ratios $R : X_1 : X_2 : Y_1 : Y_2$ are $1 : \alpha/k : \alpha\beta/k^2 : a/k : ab/k^2$, and if in a new system the initial values are in these ratios, all the components again increase according to the simple autocatalytic law. This may be illustrated, for example, by Y_2:

$$Y_2 = \frac{1}{3}\frac{ab}{k^2}\left\{R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0\right\}e^{kt}$$
$$+ \frac{ab}{\sqrt{3}k^2}\left\{-R_0 + \frac{abc}{k^3}R_0 + \frac{\alpha\beta\gamma}{k^3}R_0\right\}e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt$$
$$+ \frac{1}{3}\frac{ab}{k^2}\left\{-R_0 - \frac{abc}{k^3}R_0 - \frac{\alpha\beta\gamma}{k^3}R_0 + \frac{2abc}{k^3}R_0 + \frac{2\alpha\beta\gamma}{k^3}R_0\right\}e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt$$
$$+ b\alpha\beta\gamma\left\{\frac{aR_0}{k} - \frac{a}{\alpha}\frac{\alpha R_0}{k}\right\}t/k^3 + \alpha\beta\gamma\left\{\frac{ab}{k^3} - \frac{ab}{\alpha\beta}\cdot\frac{\alpha\beta}{k^3}\right\}$$

and since $$k^3 = \alpha\beta\gamma + abc$$

$$Y_2 = \frac{ab}{k^2}R_0\,e^{kt} + 0 + 0 + 0 + 0 = (Y_2)_0 e^{kt}$$

Lag Phenomena.—The principal interest is now in the early stages of growth in a new medium. Let us suppose that the cells have been grown for a long time in a medium in which a and b are zero, and that a sample is then transferred to a new medium in which a and b as well as α and β are finite. The initial values of the various quantities will be

$$(X_1)_0 = (\alpha/k_1)R_0,\ (X_2)_0 = (\alpha\beta/k_1^2)R_0,\ (Y_1)_0 = 0,\ (Y_2)_0 = 0,$$

where $\alpha\beta\gamma = k_1^3$, these being the proportions established after a long time in the first medium.

Growth in the new medium now conforms to the equations:

$$X_2 = \frac{1}{3}R_0\frac{\alpha\beta}{k^2}\left(1 + \frac{\alpha\beta\gamma}{k_1k^2} + \frac{\alpha\beta\gamma}{k_1^2k}\right)e^{kt} + \frac{1}{\sqrt{3}}R_0\frac{\alpha\beta}{k^2}\left(-1 + \frac{\alpha\beta\gamma}{k_1k^2}\right)e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt +$$
$$\frac{1}{3}R_0\frac{\alpha\beta}{k^2}\left(-1 - \frac{\alpha\beta\gamma}{k_1k^2} + \frac{2\alpha\beta\gamma}{k_1^2k}\right)e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt + \frac{\beta abc}{k^3}\left(\frac{\alpha}{k_1}R_0\right)t + \frac{abc}{k^3}\left(\frac{\alpha\beta}{k_1^2}\right)R_0 \quad . \quad (8a)$$

$$Y_2 = \frac{1}{3}R_0\frac{ab}{k^2}\left(1 + \frac{\alpha\beta\gamma}{k_1k^2} + \frac{\alpha\beta\gamma}{k_1^2k}\right)e^{kt} + \frac{1}{\sqrt{3}}R_0\frac{ab}{k^2}\left(-1 + \frac{\alpha\beta\gamma}{k_1k^2}\right)e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt +$$
$$\frac{1}{3}\frac{R_0ab}{k^2}\left(-1 - \frac{\alpha\beta\gamma}{k_1k^2} + \frac{2\alpha\beta\gamma}{k_1^2k}\right)e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt - \frac{ab}{k^2}\frac{\alpha\beta\gamma}{k_1k^2}R_0kt - \frac{ab}{k^2}\cdot\frac{(\alpha\beta\gamma)}{k_1^2k}R_0 \quad . \quad . \quad (8b)$$

as is found by insertion of the above zero-time values in equations (7*d* and *e*).

The initial rate of growth in the new medium may be found by expansion of the last two expressions to the first power of t, that is by substituting

$$e^{kt} = 1 + kt,\ e^{-\frac{1}{2}kt}\sin\frac{\sqrt{3}}{2}kt = (1 - \tfrac{1}{2}kt)\frac{\sqrt{3}}{2}kt = \frac{\sqrt{3}}{2}kt,\ \text{and}\ e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt = (1 - \tfrac{1}{2}kt)\times 1 = (1 - \tfrac{1}{2}kt).$$

From (8*a*) the coefficient of the first power of t is then found to be

$$\frac{\alpha\beta R_0}{k_1} = \frac{\alpha\beta R_0}{k_1^2}k_1 = (X_2)_0k_1.\quad \text{Thus initially } X_2 = (X_2)_0k_1t.$$

From 8(*b*), on the other hand, the coefficient of the first power in t in the expansion is zero, and only the quadratic term has a finite coefficient. Thus, while X_2 begins to increase at a rate similar to that prevailing in the old medium, Y_2 shows an initial rate of increase of zero, that is, its formation is attended with a lag.

This result, although a simple one, is of some importance in principle, in that it clarifies in an elementary case how of two competing processes in a single system one may lag behind the other even when the basic requirements for its operation are present.

The result which follows from equations (8*a* and *b*) may now be contrasted with that given by (6*b* and *c*) for the simpler branched system where the branches only contain one member. Here, although $(Y_1)_0$ would be zero after transfer from a medium where a and b are zero, the formation of Y_1 in the new medium sets in immediately. Thus in the earliest stages the coefficient of the first power of t in any expansion for Y_1 is not zero. The addition of an extra member to the branch makes the first power vanish, and the addition

of yet another member, it is safe to conclude, would make the first finite term in the expansion the cube in t. Thus if there is a rather elaborate network, the final members of the sequence will only be formed after very considerable lags. In the meantime the members of the alternative sequence will be formed, although not at maximum rate, at least in a progressive and continuous manner. Growth of the whole system will thus occur, but at a rate which does not attain its optimum value till the long induction period associated with the development of the extra branch of the complete reaction pattern is over.

In such circumstances the growth rate will continue for a considerable time at a lower value, and then show a rather rapid transition to a higher value.

Experimental Analogies.—The idea of alternative and competing reaction patterns, one of which may be out of use until after the lapse of a lag during which the other operates alone, is of great help in the interpretation of many experimental observations. It has been invoked, with less definite theoretical basis than the foregoing, to explain the supersession of a slower mode of growth by a faster revealed in certain segmented growth curves (" Chemical Kinetics of the Bacterial Cell," Oxford Univ. Press, 1946, pp. 180 *et seq.*). It can also explain some rather surprising phenomena observed when bacteria are transferred from one medium to a second and then later back to the first, *e.g.*, kept for a long time in glucose, then in acetate or succinate, and then taken back to glucose. In the acetate or succinate their growth is much slower, and on retransfer they sometimes grow in the glucose much more slowly than they did originally, but then slowly recover their original capacity. The retraining process may require quite a long time, though continuous growth in the glucose occurs. The more efficient reaction pattern is not established in preference to the less efficient one although it exists throughout as a potentiality.

The glucose in this example provides a large variety of intermediates in the cycle by which it is metabolised, more presumably than substances such as acetic acid can do. We may therefore apply the analogy of the example where α, β, a, and b are all finite (preceding section). In the poorer medium we will suppose a and b to be zero. On the retransfer to the glucose medium there will thus be the kind of lag discussed above.

Sometimes there is another very curious effect, namely, a violent fluctuation in the growth rate from one subculture to the next during the retraining process. These fluctuations finally disappear, and quite steady conditions return. They are characteristic in many cases of the lag in the establishment of the new reaction pattern. Not until this is over will the growth rate in the glucose regain its original value. The reason why this lag may be so long that many generations of growth by the imperfect mechanism have time to occur is a special question which will be dealt with below, together with the question of the instability of the growth rate when it is recovering towards the optimum.

Another example of long-continued growth by a less efficient mechanism eventually succeeded by a more efficient one occurs in the retraining to utilise a simple synthetic medium of cells which have been exposed to ultra-violet light (Dean and Hinshelwood, *J.*, 1951, 1169).

A significant observation is that made on the training of *Bact. lactis aerogenes* to utilise D-arabinose (Jackson and Hinshelwood, *Trans. Faraday Soc.*, 1947, **44**, 568) : continuous culture of the cells in another sugar prevents the growth in arabinose which would, in the absence of the second sugar, supervene after a day or so of lag. Here it seems that the growth by the route available in presence of, for example, glucose, actually consumes something required for the establishment of the alternative arabinose route. An analogous inhibition of one mechanism by the consumption of a necessary substance in a competing mechanism probably occurs also in the Pasteur effect.

If one of the competing reaction patterns considered in the previous sections can destroy a metabolite required by the other, then highly unstable conditions can arise. These will be discussed further in the next section.

Metabolic Interference.—We suppose there to be two enzymic components (X and Y) of the cell, in amounts X and Y respectively. Y requires some diffusible intermediate the concentration of which in any cell is c. c may be taken to reach a stationary value by the balance of formation, consumption, and loss by diffusion. Let n be the total number of cells at time t. In a given cell the intermediate is formed at a rate A, lost by diffusion

from the cell at a rate Bc, and uselessly destroyed by X at a rate CcX/n, the last being necessarily proportional not to the total amount of X but to the amount in any one cell. (Destruction of substances by enzymes without cell growth is of course a familiar occurrence.) We have then :

$$\mathrm{d}c/\mathrm{d}t = A - Bc - CcX/n = 0$$

whence $$c = \frac{A/B}{1 + \gamma X/n}, \text{ where } \gamma = C/B$$

The rates of increase of X and Y are then given by

$$\mathrm{d}X/\mathrm{d}t = k_X X, \qquad \mathrm{d}Y/\mathrm{d}t = \frac{k_Y Y}{1 + \gamma X/n}$$

The changes in the ratio $Y : X$ are shown by

$$\frac{\mathrm{d}(Y/X)}{\mathrm{d}t} = \frac{1}{X}\frac{\mathrm{d}Y}{\mathrm{d}t} - \frac{Y}{X^2}\frac{\mathrm{d}X}{\mathrm{d}t}$$

whence $$\frac{1}{(Y/X)}\frac{\mathrm{d}(Y/X)}{\mathrm{d}t} = \frac{d\ln(Y/X)}{\mathrm{d}t} = \frac{k_Y}{1 + \gamma X/n} - k_X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

If, at $t = 0$, $\dfrac{k_Y}{1 + \gamma X_0/n_0} < k_X$, then Y decreases relatively to X from the start and never recovers. If, however, $\dfrac{k_Y}{1 + \gamma X_0/n_0} > k_X$ then Y begins to increase relatively to X, but the rate of increase falls as X itself increases. A limit is set to the change in equation (9) by the fact of cell division. If X is, in the initial state of the cells, the dominant component compared with Y, then division will be governed by X, and X and n will be proportional to one another in the steady state. Suppose then that $X/n = \beta$, then the right-hand side of equation (9) becomes $k_Y/(1 + \beta\gamma) - k_X$. If this is negative, Y loses in the race and there can be no training to Y.

Suppose, however, that X_0 is so small that not only is $k_Y/(1 + \gamma X_0/n) > k_X$, but that Y increases enough to provoke division of the cell before X has increased enough to reverse the sign of equation (9); then we shall have $Y/n = \beta'$ and now

$$\frac{d\ln(Y/X)}{\mathrm{d}t} = \frac{k_Y}{1 + \beta'\gamma(X/Y)} - k_X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

If X_0 is small enough, expression (10) can start positive so that Y gains on X. As this happens, X/Y decreases so that (10) becomes still more positive and thus the race is won by Y. But the condition that expression (10) can come into operation at all is that the initial amount (or activity) of X should be sufficiently reduced.

Now the activities of all enzymes are much modified by ageing (and for this purpose an enzyme reduced in activity may be regarded as equivalent to one reduced in mass at constant activity), so that both X and Y during periods of non-proliferation of the cells will decrease, each at its own rate. We may therefore envisage in special cases short periods of growth with Y gaining on X, followed by periods of rest when the activities change in such a way that X can regain some of its preponderance during the next subculture. There will be at some stage an extremely unstable state where the two alternative reaction patterns are fairly evenly balanced and where fluctuations in growth rate will occur from one subculture to the next.

This is very similar to what is observed in some training experiments. Moreover, training to optimum growth in a medium already supporting growth by a less efficient mechanism occurs more readily if the cells are allowed periods of rest (Dean and Hinshelwood, *loc. cit.*). Examples of wide fluctuations in growth rate (not attributable to any experimental inaccuracy) are also given by Mims and Hinshelwood (*J.*, 1953, 663). Mutation and selection would hardly account for such rapid fluctuations.

It must also be remembered that the cell processes are organised in space as well as in time (cf. *op. cit.*, p. 23; Pontecorvo, Symposia Soc. Exp. Biol., 1952, VI, 218). If the intermediate to be used by Y has previously to diffuse through a region in which X is already established, there will be quite an effective inhibition of the more efficient mechanism by a less efficient but previously established one.

In conclusion it should be emphasised that the properties of autosynthetic systems here discussed are of interest in their own right and that no attempt is made in this place

to deal directly with the question of how far the analogies which they present with real biological systems may be more, or less, satisfactory than theories based upon selection. The kind of investigation attempted here is, however, a necessary preliminary to such a decision.

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263. *Boundaries Between Some Aqueous Fatty Sols and Water.*

By L. SAUNDERS.

Sharp boundaries formed between clear aqueous sols of some fatty materials solubilized by polyethylene oxide esters of stearic acid, and water, have been studied with the Gouy diffusion apparatus. The esters had small mean diffusion coefficients (D) of the same order as those of serum albumens; solubilized oleic acid increased D, but solubilized stearic acid and cholesterol decreased D slightly. No stable sol–water interfaces were formed with these materials.

A lecithin sol, clarified with one of the esters, had a small mean value of D which decreased markedly with time; a lecithin sol clarified with a small amount of bile salt gave still lower results for D which decreased after 3 days to a remarkably small value, the clarified sol–water boundary then being still clearly visible, though diffuse.

Some measurements have been made of the pull exerted on a platinum ring when it was drawn slowly up through a stable, turbid lecithin sol–water interface. A mean pull of 0·2 dyne/cm. was found for the lecithin sol alone. When a small quantity of a serum albumen sol was injected just above the interface and the boundary was allowed to mature for 20 hours before the ring was drawn through it, the pull was found to have increased to 0·8 dyne/cm., an effect which is attributed to a tanning of the lecithin film by an unfolded protein film. These pulls are of the same order of magnitude as the experimentally determined surface forces of living cells.

STUDIES have been made of the changes with time of sharp boundaries formed between some aqueous sols and water. The apparatus and methods used to form and examine these interfaces have already been described (*J.*, 1953, 519). In order to follow changes at the boundaries by the Gouy interference method it is necessary to have optically clear sols; to achieve this, polyethylene oxide stearates have been used as solubilizing agents. In contrast to the ionic soaps, these esters have been found to have low diffusion coefficients in aqueous solution, of the same order as serum albumen, as would be expected if their solutions contain electrically uncharged micelles.

EXPERIMENTAL

Materials.—Polyethylene oxide stearate A (ester A) had a setting point, *i.e.*, the constant temperature reached after supercooling, of 42·4°; its mean molecular weight, determined cryoscopically in benzene, was 2101; its loss in weight on heating at 110° was 0·5%. Polyethylene oxide stearate B (ester B), containing a lower proportion of ethylene oxide than A, had a setting point of 30·7°, M 1001, and a loss on heating at 110° of 0·8%.

Redistilled oleic acid had n_D^{25} 1·458; purified stearic acid was fractionally frozen to give acid of m. p. <69°; cholesterol had m. p. 148·5°.

Diffusion Coefficients.—Sols were freshly prepared before each measurement by melting the ester, adding to it the insoluble fatty material, and dispersing the clear liquid so obtained in warm conductivity water.

The sol–water boundary was formed in an all-glass cell as previously described (*loc. cit.*); diffusion from the interface was followed by photographing Gouy interference patterns at suitable intervals. The patterns obtained with these slow-diffusing materials showed some anomalies in the earlier stages of diffusion, and long exposures were required to obtain clear records of the outer fringes. In the later stages of diffusion, regular patterns were obtained which could be interpreted quite accurately by Kegeles and Gostling's theory (*J. Amer. Chem. Soc.*, 1947, **69**, 2516). The mean diffusion coefficients calculated for slower-diffusing materials seem to be liable to a greater percentage error than those for more rapidly diffusing compounds,

such as glycine. In the following Table, the uncertainty in D, the mean diffusion coefficient in C.G.S. units, is of the order of $\pm 2\%$.

Mean diffusion coefficients for fatty sols into water at 25°.

Expt. no.	Solubilizing ester *	Solubilized material	$D \times 10^7$	Time interval, hours
1	A 2·41	—	$5{\cdot}4_6$	½—2
2	A 4·79	—	$5{\cdot}6_0$	½—2
3	A 10·44	—	$5{\cdot}5_5$	½—2
4	A 2·09	Oleic acid 0·52	11·6	½—2
5	B 3·92	—	$5{\cdot}8_8$	½—2
6	B 4·44	—	$5{\cdot}8_4$	1—4
7	B 4·07	Oleic acid 0·88	10·3	½—2
8	B 4·35	Stearic acid 0·79	$4{\cdot}1_5$	½—2
9	B 5·02	Stearic acid 0·34	4·5	1—5
10	B 4·36	Cholesterol 0·53	$3{\cdot}9_8$	½—2
11	B 1·97	Lecithin 4·10	1·1	6
		,, ,,	0·2	70

* Numbers are g. per l. in sol.

After overnight storage, all the boundaries had an extremely diffuse appearance, except in Expt. 11.

The first three results in the Table show that the mean value of D for ester A does not vary very much with concentration and is comparatively low; if the ester is assumed to be associated into spherical micelles in the solution, this value of D corresponds to a micelle "molar volume" of $2{\cdot}1 \times 10^5$ ml. *i.e.*, each micelle contains about 105 ester molecules. Expt. 4 shows that oleic acid increases D very considerably, suggesting that the unsaturated acid molecules do not fit into the ester micelles without disrupting them.

Expts. 5 and 6 show that ester B diffuses a little more rapidly than A; D corresponds to a micelle "molar volume" of $1{\cdot}8 \times 10^5$, *i.e.*, a micelle of 185 molecules. Expt. 7 shows that the disruption of the micelles by oleic acid occurs also with ester B. Expts. 8 and 9 suggest that solubilized stearic acid enters into the ester micelles, increasing their size and lowering D. Expt. 10 shows that cholesterol behaves similarly. Expt. 11 records a measurement carried out with a lecithin sol clarified with a minimum amount of ester B. The lower fringes of the Gouy patterns were not recorded clearly until 6 hours after the start of diffusion, even when exposures of several minutes were made. The pattern at 6 hours conformed with Kegeles and Gostling's theory and gave a value of $D = 1{\cdot}1 \times 10^{-7}$ After 70 hours a well-spaced pattern still persisted, which on analysis gave $D = 2 \times 10^{-8}$.

A further measurement was made, in which a lecithin sol was clarified with a minimum amount of the most effective agent for this purpose, *viz.*, reprecipitated bile salt (Valette, *Bull. Soc. Chim. biol.*, 1937, **19**, 1676). The final sol consisted of 3·75 g./l. of lecithin and 0·25 g./l. of bile salt. After 3 days, a definite, but diffuse boundary was still visible, in line with the cell channel. Diffusion did, however, occur, as was revealed by the Gouy photographs. The individual patterns could again be fitted quite well by theory, but the values of D obtained from them decreased markedly with time; after 70 hours D was $7{\cdot}8 \times 10^{-9}$, a much smaller diffusion coefficient than those recorded for most colloidal materials. An idea of the size of the diffusing units implied by such a small coefficient is obtained by comparing it with values of D for other bio-colloids; *e.g.*, hæmocyanin with a diffusing unit "molecular weight" of 6,800,000 has $D_{20} = 1{\cdot}4 \times 10^{-7}$ (Alexander and Johnson, "Colloid Science," Vol. I, Oxford, 1949, p. 288), while a thromboplastic lung lipoprotein, where particles were shown by electron microscopy to consist of spheres of mean diameter 100 mμ, had $D_{20} = 3{\cdot}8 \times 10^{-8}$ (Chargaff, Moore, and Bendich, *J. Biol. Chem.*, 1942, **145**, 593).

Gouy patterns obtained with clarified lecithin sols.

$j_m = 8{\cdot}78$ $t = 1{\cdot}152 \times 10^4$ sec. $t = 2{\cdot}498 \times 10^5$ sec.

j	$f(z)$	e^{-z^2}	Y	C_t	Y	C_t
1	0·199	0·607	0·607	1·000	0·607	0·494
2	0·313	0·478	0·483	1·010	0·483	0·472
3	0·427	0·369	0·371	1·005	0·371	0·458
4	0·541	0·273	0·268	0·982	0·268	0·470
5	0·655	0·190	0·184	0·979	0·184	0·462
6	0·769	0·117	0·116	0·992	0·116	0·483

$\bar{C}_t = 0{\cdot}991$ $\bar{C}_t = 0{\cdot}473$

$t\bar{C}_t^2 = 1{\cdot}14 \times 10^4$ $t\bar{C}_t^2 = 5{\cdot}59 \times 10^4$

$D = 3{\cdot}8 \times 10^{-8}$ $D = 7{\cdot}8 \times 10^{-9}$

For the meaning of the symbols, see *J.*, 1953, 519.

This decrease of D with time may be due to the formation of a film structure at the interface, and this effect will be further investigated. One important feature of these slowly diffusing fatty sols, including the lecithin sols, is that their relative viscosities at 25° as determined by an Ostwald viscometer are all appreciably less than unity (*i.e.*, 0·7—0·85).

The results recorded here do not indicate any possibilities of forming stable fatty membranes between aqueous liquids, without the use of lecithin; only lecithin notably decreases the mean

diffusion coefficient of the ester. To complete this stage of the work, some measurements of the mechanical properties of lecithin films between aqueous liquids have been made.

Mechanical Properties of Lecithin Films.—These have been studied in a preliminary way by means of a ring-pull interfacial tension apparatus modelled on that decsribed by Harkins and Jordan (*J. Amer. Chem. Soc.*, **1930**, **52**, 1756), a jack and a chainomatic balance being used to raise the ring.

The boundary was formed in the diffusion cell between a 0·5% turbid lecithin sol and conductivity water, with the ring freely suspended in the sol about 5 mm. below the interface. After the sol and water had been run in from pipettes, the boundary was sharpened by flow in the usual way. The flow was then stopped, and the ring raised very slowly through the boundary. While it passed through the sol, no pull on the ring was experienced (to within $\pm$ 0·2 mg.), but on reaching the sol–water boundary a very definite pull of the order of 2 mg. occurred. As the ring came through the boundary, the balance pointer swung sharply over just as in an ordinary interfacial-tension measurement. The interfacial pull was reproducible to within $\pm$0·2 mg. and was independent of the time, up to 20 hr., for which the boundary was allowed to stand after flow had stopped. Pulling the ring through the interface caused comparatively little disturbance, and on lowering the ring into the lecithin sol layer and drawing it up through the boundary again, the same value of the interfacial pull was obtained, suggesting that the film is rapidly re-formed after being broken.

The author (*loc. cit.*) has reported a visual observation that injection of a protein sol above a lecithin sol–water interface improves the mechanical properties of the boundary. This has been confirmed by the ring-pull method. The lecithin sol–water interface was prepared, as above, and 0·1 ml. of a 0·5% bovine serum albumen (Armour Laboratories, recrystallised material) sol was injected from an Agla microsyringe, a few mm. above the interface. When the ring was raised through the boundary, soon after the injection of protein, an unchanged interfacial pull of 2 mg. was obtained. In a subsequent experiment the boundary was allowed to mature for 20 hours, before the ring was pulled through it; the interfacial pull was then very considerably increased. Four repeat measurements gave values between 7·7 and 8·5 mg. When the ring was lowered back into the sol layer and then drawn through the boundary again, low results were obtained unless the boundary was left to settle for an hour of two, suggesting that the protein-reinforced film is not re-formed rapidly after rupture.

These interfacial pulls, like the interfacial " tensions " between a living cell and its environment, are measures of the mechanical properties of interfacial films rather than of true liquid–liquid interfacial tensions.

On the basis of the crude ring-pull theory, *viz.*, pull on ring = 2 $\times$ ring circumference $\times$ interfacial tension, " tensions " for the lecithin sol–water interface of 0·2 dyne/cm., and for the protein-reinforced interface of 0·8 dyne/cm., are obtained. It is noteworthy that these values are of the same order as those found experimentally for the surface forces of living cells, *e.g.*, 0·2 dyne/cm. for *Arbacia punctulata* (Harvey, *Trans. Faraday Soc.*, **1937**, **33**, 943) and a maximum value of 1·4 dyne/cm. for nucleated erythrocytes (Norris, *J. Cellular Comp. Physiol.*, **1939**, **14**, 117).

Further studies of these interfacial film " tensions " will be made with more sensitive apparatus.

Discussion

The formation of stable boundaries at the aqueous sol–water interface has not been observed with fatty sols other than lecithin. An explanation for the film-forming properties of lecithin can be found by examining its molecular structure. From a molecular model of an α-lecithin, it can be seen that this compound is able to assume a configuration in which the fatty chains are parallel and the negatively charged oxygen atom of the phosphate group lies directly below one fatty acid chain while the positively charged nitrogen atom of the choline group lies directly below the other. In this arrangement, the lecithin molecules will readily form stable laminar micelles in water, the hydrophobic chains forming the interior of the micelle leaving the hydrophilic, electrically charged parts of the molecules facing outwards towards the water on either side of the micelle. Further stabilization can be expected by interaction between the choline group of one molecule and the phosphate group of its neighbour.

The mechanical shearing effect produced by the flowing of the lecithin sol against water in the diffusion cell seems to play a necessary part in the production of a large stable film; the sol itself mixes quite freely with water under normal conditions.

The sheet of dipoles left facing the water will provide a surface which will readily

adsorb amphoteric materials with a similar zwitterionic structure. This may lead to the joining of several bimolecular sheets into a thick film. The enhanced mechanical strength of lecithin films after treatment with protein is probably due to a tanning process in which the zwitterionic lecithin sheet unfolds the amphoteric protein molecules into a surface-denatured form. This is likely to be a slow process, as is found experimentally.

The observation, reported previously (*loc. cit.*), that a stable boundary is not formed between a lecithin sol and a serum albumen sol, indicates that it is necessary to have the lecithin film already in existence before the protein can be adsorbed; the presence of protein inhibits formation of this film, possibly by combining to form a lecithin–protein complex in which the protein molecules are still in the folded form.

It is to be expected that synthetic zwitterionic compounds containing fatty acid groups and appropriately spaced charged groups will have film-forming properties similar to those of lecithin.

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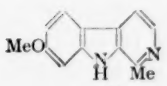
NOTES.

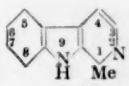
264. *Synthesis of* 5 : 6 : 7 : 8-*Tetrahydro*-1-*methyl*-β-*carboline.*

By G. R. CLEMO and R. J. W. HOLT

IT is somewhat surprising that *apo*harmine (I) the important degradation product of harmine (II) has apparently not been synthesised directly although Lawson, Perkin, and Robinson (*J.*, 1924, **626**) state that by degradation of synthetic methyldiveratroharmyrine enough *apo*harmine was obtained for a comparison of melting points and fluorescent properties.

(I)


(II)


(III)

We have prepared the 2-methyl-3-pyridylhydrazones of ethyl pyruvate and *cyclo*hexanone, but so far have not cyclised the former by the Fischer method, although the latter readily gives the hitherto undescribed 5 : 6 : 7 : 8-tetrahydro-1-methyl-β-carboline (III) which has been dehydrogenated to harman.

This appears to be the first successful use of the Fischer indole reaction in the pyridine series and also of the synthesis of the harman system starting with its pyridine ring, and although our work is incomplete we record it in view of the work of Baumgarten and Su (*J. Amer. Chem. Soc.*, 1952, **74**, 3828).

Experimental.—*6-Amino-2-methyl-3-nitropyridine.* 6-Amino-2-picoline (81 g.) was added with stirring to nitric acid (50 c.c.; *d* 1·42); the solid nitrate was washed with acetone (50 c.c.). The dry nitrate (100 g.) was added to cooled concentrated sulphuric acid (400 c.c.) with stirring, the solution heated at 100° for 1 hour, then cooled, 20% oleum (30 c.c.) added, and the whole heated at 100° for a further hour. 6-Amino-2-methyl-3-nitropyridine (Siede, *J. Russ. Phys. Chem.*, 1918, **50**, 534) was obtained from the reaction mixture and converted into the 6-chloro-compound (Baumgarten and Su, *loc. cit.*).

3-Amino-2-methylpyridine (cf. Parker and Shive, *J. Amer. Chem. Soc.*, 1947, **69**, 63). 6-chloro-2-methyl-3-nitropyridine (40 g.) was shaken in methanol (1 l.) under hydrogen at room temperature and pressure with palladised charcoal (2 g.; 15%), the catalyst and methanol were removed and the 3-amino-2-methylpyridine (22 g.) was obtained from the residue by basification and extraction with hot benzene.

2-Methyl-3-pyridylhydrazine. 3-Amino-2-methylpyridine (10 g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and cooled to −20°, solid sodium nitrite (7 g.) added during 2 hours, and the mixture kept at −20° for a further 2 hours and then added dropwise to a stirred solution of stannous chloride (50 g.) in concentrated hydrochloric acid (35 c.c.) at −20°. The

mixture was left overnight, the solid collected, and the 2-*methyl*-3-*pyridylhydrazine* liberated by basification and extraction with ether; it separated from benzene as yellow needles (2·5 g.; m. p. 130—131°) (Found: C, 58·25; H, 7·3. $C_6H_9N_3$ requires C, 58·5; H, 7·3%).

Ethyl pyruvate 2-*methyl*-3-*pyridylhydrazone*. The foregoing hydrazine (1 g.) and ethyl pyruvate (1 g.) were mixed and pyridine (2 c.c.) was added. The mixture was heated on a water-bath for 0·5 hour, and water (4 c.c.) added. The *hydrazone* separated on cooling and recrystallised from aqueous alcohol as almost colourless needles (1·4 g.), m. p. 119—120° (Found: C, 60·0, 59·9; H, 7·2, 7·2. $C_{11}H_{15}O_2N_3$ requires C, 59·8; H, 6·8%).

cyclo*Hexanone* 2-*methyl*-3-*pyridylhydrazone*. The hydrazine (1 g.) and *cyclo*hexanone (1 g.) gave the hydrazone (1·5 g.), m. p. 128—129° (Found: C, 71·0; H, 8·6. $C_{12}H_{17}N_3$ requires C, 71·0; H, 8·4%).

5 : 6 : 7 : 8-*Tetrahydro*-1-*methyl*-β-*carboline*. *cyclo*Hexanone 2-methyl-3-pyridylhydrazone (1 g.), zinc chloride (5 g.), and dry ethanol (5 c.c.) were heated at 100° during 18 hours in a sealed tube; the reaction mixture was evaporated to small bulk, basified, and extracted with ether. The *carboline* (0·1 g.), crystallised from benzene–acetone and then sublimed at 160°/16 mm., had m. p. 233—235° (Found: C, 76·95; H, 7·7; N, 14·8%; *M*, 182·5. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·5; N, 15·0%; *M*, 186).

Harman. The carboline (0·01 g.), palladised charcoal (0·005 g., 15%), and Dowtherm (diphenyl ether 75%, diphenyl 25%) (0·2 c.c.) were refluxed for 1 hour, benzene was added, and the mixture extracted with 2N-hydrochloric acid. The acid solution showed blue-violet fluorescence in ultra-violet light. On basification and extraction, harman (0·007 g.) was obtained as colourless crystals (from benzene), m. p. 237—238°, depressed to 210° by the tetrahydro-compound but unchanged by admixture with an authentic specimen of harman (Found: C, 79·3; H, 6·0. Calc. for $C_{12}H_{10}N_2$: C, 79·0; H, 5·5%).

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NEWCASTLE-ON-TYNE.

[*Received, December 6th*, 1952.]

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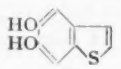
265. *The Synthesis of* 5 : 6-*Dihydroxythionaphthen.*

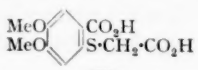
By D. G. BEW and G. R. CLEMO.

IN view of work in progress on the formation of melanin from 5 : 6-dihydroxyindole, 5 : 6-dihydroxythionaphthen (I) has been prepared and its oxidation examined.

6-Nitroveratric acid was converted *via* the derived amino-ester into the substituted thiosalicylic acid and thence into (2-carboxy-4 : 5-dimethoxyphenylthio)acetic acid (II), but the cyclisation of this by acetic anhydride (Hansch and Lindwall, *J. Org. Chem.*, 1945, **19**, 383) and alkali fusion (Friedlander, *Annalen*, 1907, **351**, 406) to the thioindoxyl (III; R = H) proved troublesome. The diethyl ester of (II), however, was readily cyclised by sodium in toluene to ethyl 5 : 6-dimethoxythioindoxyl-2-carboxylate (III; R = CO_2Et). This proved surprisingly resistant to both acid and alkaline hydrolysis.



(I)



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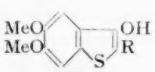
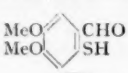


(III)

Attention was then turned to the preparation of the 4 : 5-dimethoxy-2-mercaptobenzaldehyde (IV) by direct replacement from the 2-bromo-aldehyde (cf. Fries and Hemmecke, *Annalen*, 1927, **454**, 126; Hemmecke, Diss., Braunschweig, 1929) but without success, and the thiol was ultimately obtained from 6-aminoveratraldehyde (cf. Bogert and Elder, *J. Amer. Chem. Soc.*, 1929, **51**, 526) by diazotisation and coupling with potassium ethyl xanthate followed by hydrolysis. Condensation of (IV) in alkaline solution with chloroacetic acid gave (V) which on liberation cyclised spontaneously to 5 : 6-dimethoxythio-



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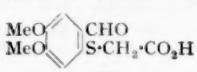

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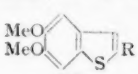

(VI)

naphthen-2-carboxylic acid (VI; R = CO_2H). This was decarboxylated by the method of Shepard, Winslow, and Johnson (*J. Amer. Chem. Soc.*, 1930, **52**, 2083) to 5 : 6-dimethoxythionaphthen (VI; R = H). Demethylation by anhydrous pyridine hydrochloride (Prey,

Ber., 1941, **74**, 1221) gave the desired compound (I). This is markedly more stable to oxidation than its nitrogen analogue but its solution in 2N-sodium hydroxide rapidly becomes dark brown and gradually deposits a brown solid. Aeration in solution at pH 8 did not lead to the evolution of carbon dioxide (cf. Clemo, Duxbury, and Swan, *J.*, 1952, **3464**).

Experimental.—Ethyl 6-aminoveratrate. The nitro-ester (Fetscher and Bogert, *J. Org. Chem.*, 1939, **4**, 71) (10 g.) and Raney nickel (5·5—6 g.) in ethanol (150 ml.) were stirred with hydrogen at 100°/100 atm. for 6 hours, then filtered and concentrated under reduced pressure, and the hydrochloride (8·1 g.; m. p. 201—203°) was precipitated with hydrochloric acid.

(*2-Carboxy-4 : 5-dimethoxyphenylthio)acetic acid* (II). To the above hydrochloride (5 g.) in water (50 ml.) and 2N-hydrochloric acid (15 ml.), sodium nitrite (3·0 g.) in water (10 ml.) was added dropwise with cooling. The diazonium solution was added slowly to a stirred solution of potassium ethyl xanthate (4·0 g.) and sodium carbonate (2·5 g.) in water (50 ml.) at 70°. On cooling, the dark brown oil which separated was extracted with ether and refluxed for 2 hours with sodium hydroxide (3·5 g.) in water (5 ml.) and methanol (40 ml.). A solution of chloroacetic acid (1·5 g.) in water (5 ml.) basified with sodium carbonate was added and refluxing continued for 2 hours. The methanol was removed, the solution treated with charcoal, and the *acid* (II) precipitated by hydrochloric acid. Sublimation or recrystallisation from alcohol gave a cream-coloured solid (1·8 g.; m. p. 229—230°) (Found: C, 48·6; H, 4·9; S, 11·7. $C_{11}H_{12}O_6S$ requires C, 48·6; H, 4·4; S, 11·8%). The *diethyl* ester has m. p. 82—83° (Found: C, 54·8; H, 6·75. $C_{15}H_{20}O_6S$ requires C, 54·9; H, 6·1%).

Ethyl 5 : 6-dimethoxythioindoxyl-2-carboxylate. The diester (0·7 g.) was refluxed with powdered sodium (0·25 g.) in toluene (20 ml.) for 3 hours, excess of sodium removed with alcohol, the solution acidified (hydrochloric acid) and taken to dryness, and the residue taken up in water (10 ml.) and extracted with ether, giving a pale brown *ester* which recrystallised from alcohol in plates (0·35 g.), m. p. 137—138° (Found: C, 55·3; H, 5·3. $C_{13}H_{14}O_5S$ requires C, 55·3; H, 5·0%).

5 : 6-Dimethoxythionaphthen-2-carboxylic acid. To 6-aminoveratraldehyde (4·1 g.) and sodium nitrite (1·7 g.) in aqueous ethanol, a solution of sulphuric acid (4·3 ml.) in water (30 ml.) was added with cooling. The red solution was added to potassium ethyl xanthate (4·0 g.) and sodium carbonate (3·5 g.) in water (30 ml.) at 70°, the whole extracted with ether, and the dark brown oil obtained on removal of the solvent refluxed with sodium hydroxide (3·0 g.) in water (5 ml.) and methanol (20 ml.) for an hour. A solution of chloroacetic acid (1·8 g.) in water (5 ml.) made alkaline with sodium carbonate was then added and refluxing continued for an hour. The methanol was removed, the solution acidified, and the crude *acid* recrystallised from alcohol (0·6 g.; m. p. 255—257°) (Found: C, 55·7; H, 4·6; S, 13·3. $C_{11}H_{10}O_4S$ requires C, 55·4; H, 4·25; S, 13·5%).

5 : 6-Dimethoxythionaphthen. The acid (VI; R = CO_2H) (0·6 g.), quinoline (7 ml.) and copper powder (0·1 g.) were heated at 200—220° for 40 min. whilst a slow stream of nitrogen was passed in. The solution was acidified (sulphuric acid), and *5 : 6-dimethoxythionaphthen* isolated by steam-distillation as a white solid of characteristic odour (0·3 g.; m. p. 89—91°) (Found: C, 61·6; H, 5·3. $C_{10}H_{10}O_2S$ requires C, 61·9; H, 5·2%).

5 : 6-Dihydroxythionaphthen. 5 : 6-Dimethoxythionaphthen (0·2 g.) and pyridine hydrochloride (0·6 g.) were heated at 140—150° for 20 min. with exclusion of moisture. The temperature was then raised to 180—190° and heating continued for 30 min. Water (10 ml.) was added and the solution treated with charcoal and extracted with ether, and the *dihydroxythionaphthen* recrystallised from ether–light petroleum (19 mg.; m. p. 134—137°) (Found: C, 57·9; H, 4·2. $C_8H_6O_2S$ requires C, 57·8; H, 3·65%).

One of us (D. G. B.) thanks D.S.I.R. for a Maintenance Grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, December 12th*, 1952.]

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266. *Course of Cyclisation in the Formation of Alicyclic Rings. Part II.* A Paradoxical Case of Dieckmann Cyclisation.*

By R. N. CHAKRAVARTI.

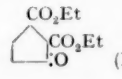
IN Part I (cf. *Experientia*, 1947, **3**, 149) it has been established that an alkyl group attached to the β-carbon atom of a polycarboxylic ester has a deactivating influence on the α-methylene group. From this it may be inferred that, owing to its negative character, a carbethoxy-group attached to the β-carbon atom of a polycarboxylic ester has an activat-

* Part I, *J.*, 1947, 1028.

ing influence on the α-methylene group. This is supported by the fact that Dieckmann cyclisation of ethyl butane-1 : 2 : 4-tricarboxylate (I) leads to a mixture of (II) and (III) in which (II) largely predominates.

(I) $EtO_2C{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$

(IV) $EtO_2C{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$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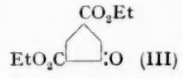
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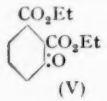
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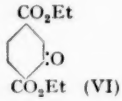
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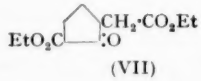
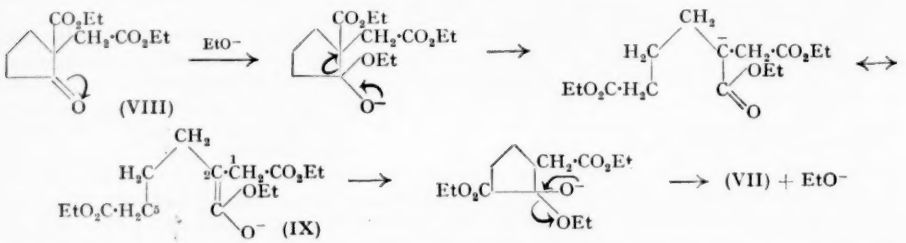

(VII)

Dobson, Ferns, and Perkin (*J.*, 1909, **95**, 2010) found that Dieckmann cyclisation of ethyl pentane-1 : 2 : 5-tricarboxylate (IV) followed by hydrolysis affords 3-keto*cyclo*hexanecarboxylic acid. Chatterjee, Das, and Barpujari later (*J. Indian Chem. Soc.*, 1940, **17**, 161) observed that ethyl 1-carbethoxy-2-keto*cyclo*pentylacetate (VIII) is transformed by hot alcoholic sodium ethoxide into the *cyclo*pentanone ester (VII). The last authors (cf. also N. K. Chakravarty and Banerjee, *ibid.*, 1946, **23**, 377) considered this to occur by



way of (IV) and erroneously concluded (cf. Atwood, Stevenson, and Thorpe, *J.*, 1923, **123**, 1758; von Braun, *Ber.*, 1928, **61**, 441; Chakravarti, *J. Indian Chem. Soc.*, 1943, **20**, 393) that the five-membered ring is almost invariably formed in preference to the six-membered ring when the two possibilities exist.

As stated above, owing to the influence of the carbethoxy-group attached to the β-carbon atom, (IV) may be expected to give (V) as major product, and (VI) and (VII) as minor products. Since both (V) and (VI) on hydrolysis give 3-keto*cyclo*hexanecarboxylic acid the experimental results of Dobson *et al.* (*loc. cit.*) can be explained. As regards the experimental results of Chatterjee *et al.* (*loc. cit.*), the reaction mechanism shown in the annexed scheme (VIII ⟶ VII) is now proposed. In other words, the latter reaction appears to proceed, not through (IV), but through the ester anion (IX).

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267. *A New Synthesis of* 2 : 5-*Dihydroxyphenyl*-DL-*alanine adapted to Isotopic Scale.*

By Alexander T. Shulgin and Emery M. Gal.

There is apparently no record of the synthesis of 2 : 5-dihydroxyphenyl-DL-alanine by condensation of a 2 : 5-dimethoxybenzyl halide with either sodioacetamidomalonic ester or sodioacetamidocyanoacetic ester, although the reactions of similar halides were extensively explored (Burckhalter and Stephens *J. Amer. Chem. Soc.*, 1951, **73**, 56), and tyrosine was obtained in excellent yields (Fields, Walz, and Rothchild, *J. Amer. Chem. Soc.*, 1951, **73**, 1000). The reported syntheses all employed free or substituted 2 : 5-dihydroxybenzaldehyde and acetylglycine (Hirai, *Biochem. Z.*, 1927, **189**, 88; Neuberger, *Biochem. J.*, 1948, **43**, 599; Lambooy, *J. Amer. Chem. Soc.*, 1949, **71**, 3758) or hippuric acid (Yakovlev,

Zhur. Obschei Khim., 1950, **20**, 361) condensation to the oxazole which is reduced with phosphorus and hydrogen iodide to 2 : 5-dihydroxyphenyl-DL-alanine. Lambooy claimed superior yields from 2 : 5-dihydroxybenzaldehyde with an overall yield of 26% whereas Yakovlev reported 40·7%.

The authors prepared diethyl α-acetamido-α-2 : 5-dimethoxybenzylmalonate and ethyl α-acetamido-α-cyano-α-2 : 5-dimethoxybenzylacetate. Unlike the derivatives described by Burchhalter *et al.* (*loc. cit.*), the above precursors failed to give 2 : 5-dihydroxyphenyl-DL-alanine on hydrolysis with 40 or 48% hydrogen bromide, in an inert or hydrogen atmosphere. Extensive charring resulted within a couple of hours. Alkaline hydrolysis was equally unsuccessful. Hydrolysis and decarboxylation with hydrogen iodide in glacial acetic acid in an inert atmosphere yielded 2 : 5-dihydroxyphenyl-DL-alanine, in overall yield of 45—49%. The chemically pure samples of 2 : 5-dihydroxyphenylalanine prepared by either this method or that of Yakovlev gave a second, weakly positive ninhydrin spot which moved ahead of the 2 : 5-dihydroxyphenylalanine in butanol–acetic acid–water.

DL-Tyrosine was similarly prepared through diethyl α-acetamido-α-*p*-methoxybenzylmalonate. The yield of ethyl α-cyano-α-*p*-methoxybenzylacetate was 70% in contrast to the 91% overall yield reported by Fields *et al.* (*loc. cit.*).

Experimental.—2 : 5-*Dimethoxybenzyl bromide.* The sample of 2 : 5-dimethoxybenzyl alcohol (2·8 g.), obtained in 75% yield through the lithium aluminum hydride reduction (Adams, Harfenist, and Loewe, *J. Amer. Chem. Soc.*, 1949, **71**, 1624) of 2 : 5-dimethoxybenzoic acid, distilling at 85—90°/25 × 10^{-3} mm. was taken up in dry (P_2O_5) carbon tetrachloride (25 ml.). Phosphorus tribromide (1·5 g.) in carbon tetrachloride (10 ml.) was slowly added to the ice-cooled solution, which was then set aside overnight at room temperature, protected from moisture. The carbon tetrachloride solution was decanted from the separated phosphorous acid residue, which was extracted with carbon tetrachloride (2 × 10 ml.), and the extracts and original solution were pooled. The solvent was evaporated from the combined original solution and extracts, and the residue was sublimed. 2 : 5-*Dimethoxybenzyl bromide* sublimed as white needles (3·29 g.; 85%; m. p. 75—76°) at 90—100° (bath-temp.)/1 mm. (Found: C, 46·9; H, 4·7; Br, 34·3. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%). The alcohol was identified as its p-*nitrobenzoate*, m. p. 110° (Found: C, 60·1; H, 4·8; N, 4·4. $C_{16}H_{15}O_6N$ requires C, 60·6; H, 4·8; N, 4·4%).

Diethyl α-acetamido-α-2 : 5-dimethoxybenzylmalonate. To the above bromide (2·38 g., 0·01 mole) an alcoholic solution of ethyl sodioacetamidomalonate (from 0·23 g. of sodium and 2·17 g. of ester; 0·01 mole) was added, the solution was refluxed for 3 hours, and the alcohol was removed under vacuum. The residue was washed with water (10 ml.) and the residue taken up in boiling water to which enough alchool was added to complete dissolution. On cooling overnight white crystals (2·8 g., 75% when dried), m. p. 84—85° of the *ester* separated (Found: C, 58·6; H, 6·6; N, 3·9. $C_{18}H_{25}O_7N$ requires C, 58·8; H, 6·85; N, 3·8%).

The *ester* obtained in a similar manner from the condensation of the bromide and ethyl acetamidocyanoacetate melted at 121° (Found: C, 60·0; H, 6·15; N, 8·9. $C_{16}H_{20}O_5N_2$ requires C, 60·0; H, 6·3; N, 8·7%).

2 : 5-*Dihydroxyphenyl-DL-alanine.* To freshly-distilled acetic acid (1·0 ml.) and freshly-distilled constant-boiling hydrogen iodide (0·8 ml.) the substituted malonic ester (250 mg.) was added, and the mixture was gently refluxed under a stream of nitrogen for 3 hours. (When necessary, small crystals of sodium hypophosphite were added until all iodine colour disappeared.) The mixture was then concentrated to dryness *in vacuo* at 50—55° (bath-temp.). The residue was dissolved in water (0·5 ml.) and again concentrated to dryness. A solution of the resulting solid (2 : 5-dihydroxyphenylalanine hydroiodide, m. p. 230—235°) in hot water (1·0 ml.) was carefully adjusted to pH 4·5 with ammonia solution, and left in the icebox for 3 days. The white crystals (95 mg., 65%) were shown to be free from glycine by paper chromatography. After recrystallization they contained 1 molecule of water of crystallisation (Found: C, 50·0; H, 6·0; N, 6·4. Calc. for $C_9H_{11}O_4N,H_2O$: C, 50·2; H, 6·1; N, 6·5%). The product, which melted over the range 230—250°, reduced phosphomolybdic acid in acid solution.

Diethyl α-acetamido-α-p-methoxybenzylmalonate. This was prepared, in 60% yield, as for the 2 : 5-dimethoxy-analogue; the *ester*, m. p. 50—51° (Found: C, 60·2; H, 6·8; N, 4·2. $C_{17}H_{23}O_6N$ requires C, 60·5; H, 6·9; N, 4·1%), gave DL-tyrosine in 80% yield on hydrolysis in glacial acetic acid and hydrogen iodide. Chromatography of the DL-tyrosine gave a single ninhydrin-positive spot of the correct R_F value.

The authors thank Professor David M. Greenberg for his interest and support of this work, which was supported by grants from the National Cancer Institute, United States Public Health Service, and the Life Insurance Medical Research Fund.

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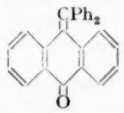
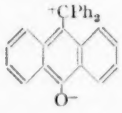
268. *The Thermochromism of Diphenylmethyleneanthrone.*

By R. J. W. LE FÈVRE and (MISS) I. YOUHOTSKY.

SCHÖNBERG, ISMAIL, and ASKER (*J.*, 1946, 442) attributed the thermochromic properties of diphenylmethyleneanthrone (I) and a number of related substances to the increasing contribution, with rise of temperature, of betaine structures (*e.g.*, II) to the hybrid real states of the molecules. Since (II), if fully developed, should have a dipole moment of 25—30 D, it seemed of interest to compare the apparent polarities of cold (pale yellow) and warm (yellow-red) solutions in benzene.

(I)   (II)

Apparatus and techniques were those used for the thermochromic *spiro*pyrans (Hukins and Le Fèvre, *J.*, 1949, 2088). Measurements are tabulated under conventional headings. The solute was prepared as noted by Padova (*Compt. rend.*, 1906, **143**, 122; *Ann. Chim. Phys.*, 1910, **19**, 386) and Clar and Müller (*Ber.*, 1930, **63**, 869). Recrystallised from glacial acetic acid it had m. p. 205—207°.

Diphenylmethyleneanthrone in benzene.

	Temp. 25°.				Temp. 55°.			
10^6w_2 *	ε^{25}	d_4^{25}	P_2 (c.c.)	n_D^{25}	10^6w_2 *	ε^{55}	d_4^{55}	P_2 (c.c.)
0	2·2725	0·87378	—	1·4972	0	2·2133	$0{\cdot}84180_5$	—
1,823	2·2817	0·87424	426	—	2·425	2·2235	0·84227	389
2,425	2·2839	0·87439	403	—	3,924	2·2298	0·84238	397
3,010	2·2868	0·87469	398	—	8,200	2·2480	0·84329	398
3,924	2·2905	0·87476	387	—	9,840	2·2555	0·84387	400
4,616	2·2926	0·87516	372	—	11,988	2·2652	0·84445	393
15,060	2·3342	0·87830	351	1·4997				

* Subscript 2 indicates solute (see footnote in *J.*, 1952, 1932).

The polarisations tabulated under P_2 have been calculated by Sugden's mixture rule (*Trans. Faraday Soc.*, 1934, **30**, 720). To obtain values at infinite dilution the observed changes of dielectric constant or density from solvent to solutions have been fitted by the method of least squares to power series in w_2, thus :

$$\text{At } 25^\circ \begin{cases} (\varepsilon_{12} - \varepsilon_1)_{w_2} = 4{\cdot}74w_2 - 43w_2^2 \\ (d_{12} - d_1)_{w_2} = 0{\cdot}269_5w_2 + 2{\cdot}0w_2^2 \end{cases}$$

$$\text{At } 55^\circ \begin{cases} (\varepsilon_{12} - \varepsilon_1)_{w_2} = 4{\cdot}11w_2 + 18w_2^2 \\ (d_{12} - d_1)_{w_2} = 0{\cdot}126w_2 + 7{\cdot}9w_2^2 \end{cases}$$

The coefficients of w_2 were taken as the $\alpha\varepsilon_1$ or βd_1 needed for the equation : ${}_\infty P_2 = M_2[p_1(1-\beta) + C\alpha\varepsilon_1]$ (cf. *J.*, 1937, 1805; *Trans. Faraday Soc.*, 1950, **46**, 1). Our results, after computation of standard errors, appear as follows :

Temp.	$\alpha\varepsilon_1$	β	p_1 (c.c.)	C	${}_\infty P_1$ (c.c.)
25°	4·74 ± 0·06	0·308 ± 0·009	0·3409	0·1881	404 ± 5
55	4·11 ± 0·02	0·150 ± 0·013	0·3421	0·2007	400 ± 3

The refractive indexes of the first five solutions (25° set) were indistinguishable from that of benzene (on the Abbé refractometer available) whence R_2 follows as $M_2\gamma_1 = 120$ c.c. However, from the strongest solution an R_2 of 113 c.c. is calculable and, being nearer the value expected (108 c.c., from anthrone 57·5 c.c., benzene 26·1 c.c., hydrogen 1·1 c.c., and carbon 2·4 c.c.), has been used in estimation of the moments. These emerge respectively as 3·77 ± 0·03 D at 25° and 3·93 ± 0·02 D at 55°.

Comment.—Despite the experimental uncertainties there is thus a slight sign that μ^{55} is greater than μ^{25}.

We originally intended the measurements in benzene to be preliminary to others with solvents with which higher temperatures could be reached. We did not proceed with this, however, after the appearance of a paper by Grubb and Kistiakowsky (*J. Amer. Chem. Soc.*, 1950, **72**, 419). These authors reported spectra of (I⟷II) in decalin from 28° to 153° and observed the (single) band at 3550 Å to cover an area which is independent of temperature although a widening and flattening of the over-all absorption curve occurred as the temperature rose. This they explain on the Franck–Condon principle, and conclude that thermochromism is here due "to a trivial cause, the broadening of a near-ultra-violet absorption region by changing distribution of molecules among vibrational states." The same hypothesis probably covers the otherwise puzzling case of the *spiro*pyrans (Hukins and Le Fèvre, *loc. cit.*; cf. however, Knott, *J.*, 1951, 3028).

The value now recorded for the moment at 25° ($3{\cdot}7_7$ D) itself indicates marked conjugative modification of the carbonyl group (compare *cyclo*hexanone, $\mu = 2{\cdot}75$ D, with 3 : 5-dimethyl*cyclo*hex-5-enone, $\mu = 3{\cdot}79$ D, or menthone, $\mu = 2{\cdot}8$ D, with piperitone, $\mu = 3{\cdot}8$ D;* indeed, where mesomeric shifts of the type $>C{=}\overset{\curvearrowright}{O}$ are concerned, it puts diphenylmethyleneanthrone beyond anthrone in the series: $Ph_2C{:}C{:}O$, $\mu = 1{\cdot}7_6$, $Ph_2C{:}O$, $\mu = 2{\cdot}9_5$, anthrone, $\mu = 3{\cdot}4_6$, diphenylmethyleneanthrone, $\mu = 3{\cdot}7_7$ D.

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, December 29th*, 1952.]

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269. *Reactions of Sodium Carbonate and Sodium Hydroxide with Dinitrogen Tetroxide.*

By C. C. ADDISON and J. LEWIS.

Reactions with Sodium Carbonate.—The observations of Oswald (*Ann. Chim.*, 1914, **1**, 44) that sodium carbonate reacts with nitrogen dioxide to give a mixture of sodium nitrate and nitrite, and of Briner, Lugrin, and Monnier (*Helv. Chim. Acta*, 1930, **13**, 64) that calcium carbonate gives calcium nitrate only on reaction with liquid dinitrogen tetroxide, would imply that the reactions differ in the liquid and in the gaseous state. This is not in agreement with conclusions reached from the study of reactions of metal oxides (Addison and Lewis, *J.*, in the press), and the reactions of sodium carbonate have therefore been reinvestigated.

Sodium carbonate was dried to constant weight at 600°. On addition of liquid dinitrogen tetroxide to the cold solid, there was no immediate visible reaction; on long standing, nitric oxide was produced in sufficient amount to turn the tetroxide clay-brown, and the liquid froze to a pale blue solid.

When the sodium carbonate had been dried at 250°, the temperature recommended for its drying for analytical purposes (see, *e.g.*, Vogel, "Quantitative Inorganic Analysis," 1st edn., Longmans, p. 281), the solid reacted vigorously, evolving nitric oxide and carbon dioxide and giving a product containing sodium nitrite also. The nitrite did not arise from adsorbed nitrogen dioxide, since the reaction product was heated at 100° for 24 hours before hydrolysis. The Table gives typical experimental results. For dry sodium carbonate,

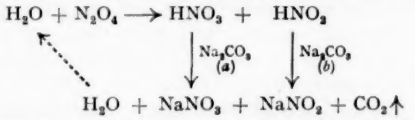
Reaction of liquid dinitrogen tetroxide with sodium carbonate

	(1) Dried at 250°		(2) Dried at 600°	
Period of contact (hours)	19	24	19	24
Conversion, %, into nitrate	49	64	10·2	14·6
Conversion, %, into nitrite	10	12·3	0·0	0·0

the reaction may be represented as $Na_2CO_3 + 2N_2O_4 = 2NaNO_3 + CO_2 + N_2O_3$. Comparisons in the table illustrate the extreme sensitivity of this reaction to traces of moisture,

* For references see the M.I.T. Tables. The value for piperitone is from Le Fèvre and Maramba (*J.*, 1952, 235) who, when writing their paper were unaware of a previous determination (omitted from the M.I.T. Tables) by Naves and Papazian (*Helv. Chim. Acta*, 1942, **25**, 1053).

which caused a considerable increase in the quantity of nitrate produced as well as introducing nitrite. This is explained by the following scheme of reactions:



From the Table, the quantities of nitrate and nitrite (formation of which may be attributed to the moisture present) are seen to be in the approximate molar ratio **4** : **1**, rather than the equimolar amounts which would result if reactions (*a*) and (*b*) in the above scheme proceeded with equal readiness. The predominance of reaction (*a*) is in accord with the known properties of nitric and nitrous acids. In media of low dielectric constant the HNO_3 molecule is largely covalent; ionic dissociation can give only the $H^+NO_3^-$ ion-pair. Nitrous acid retains its covalent character even in aqueous solution, so ionic dissociation under these conditions is much less probable. When this does occur, the formation of the NO^+OH^- ion-pair is as likely as that of the $H^+NO_2^-$ form, and there is no apparent reason why the former should undergo reaction with sodium carbonate.

Sodium carbonate (dried at **600°**) was found to react with nitrogen dioxide gas according to the equation $Na_2CO_3 + 3NO_2 = 2NaNO_3 + CO_2 + NO$; **33%** conversion into nitrate occurred after **7** hours' contact at **250°**. No nitrite was produced at any temperature. The increased reaction rate at high temperature is not due to thermal dissociation products of nitrogen dioxide, since experiments at temperatures up to **280°** and periods of contact up to **3** hours showed that sodium carbonate was quite inert to nitric oxide. Nitrogen dioxide is therefore the only gaseous oxide of nitrogen to react with sodium carbonate, since it was observed during analysis of sodium hyponitrite (*J.*, 1952, 338) that the reaction $Na_2N_2O_2 + CO_2 = Na_2CO_3 + N_2O$ proceeds rapidly in the forward direction.

Reaction with Sodium Hydroxide.—This reaction has some points of analogy with the above. Sodium hydroxide was dried by fusing it in a silver boat at **320°** for **3** hours in a current of dry oxygen. On addition of the dried hydroxide (**1** g.) to **10** ml. of liquid dinitrogen tetroxide, reaction was vigorous, causing boiling of the tetroxide, and the green coloration of dinitrogen trioxide developed round the solid. Next morning the liquid was evaporated. In an attempt to remove the remaining traces of tetroxide, the white solid product was heated at **100°** for a few minutes, and the evolved nitrogen dioxide removed by a current of dry oxygen. This is usually adequate, in the case of sodium salts, to remove adsorbed tetroxide, but in this reaction it was necessary to repeat this process several times before the atmosphere above the solid was free from nitrogen dioxide. This behaviour is attributed to decomposition of nitrous (and/or nitric) acid adsorbed on the solid. Analysis of this product showed **94%** conversion into sodium nitrate, and **2·5%** conversion into nitrite, the remainder being sodium hydroxide. The reaction may be considered as an ionic exchange: $Na^+OH^- + NO^+NO_3^- \longrightarrow Na^+NO_3^- + ON^+OH^-$. The small quantity of sodium nitrite in the reaction product indicates that the nitrous acid molecule reacts only slightly with sodium hydroxide the decomposition of nitrous acid under these conditions being responsible for the green colour observed in the liquid during reaction.

THE UNIVERSITY, NOTTINGHAM. [*Received, December 9th*, 1952.]

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270. *The Use of Iodine and Potassium Acetate in the Dehydrogenation of Tetrahydroisoquinoline. The Synthesis of 7-Nitroisoquinoline.*

By M. D. POTTER and E. P. TAYLOR.

7-NITRO*iso*QUINOLINE has recently been prepared (McCoubrey and Mathieson, *J.*, 1951, 2851) by the nitration of **3** : **4**-dihydro*iso*quinoline and catalytic dehydrogenation of the product. The overall yield of crude product was poor (**21%**), and we have found that this falls to **8**—**10%** on purification. Moreover, the starting material, **3** : **4**-dihydro*iso*quinoline, can itself be prepared only in very low yields by the Bischler–Napieralski reaction [Späth, Berger, and Kuntara, *Ber.*, **1930**, **63**, **134** (18%); Snyder and Werber, *J. Amer. Chem. Soc.*, **1950**, **72**, **2962** (31%)].

Attempts were first made to improve the preparation of the starting material. The dehydrogenation of 2-substituted 1 : 2 : 3 : 4-tetrahydro- to 3 : 4-dihydro-*iso*quinolines by iodine and potassium acetate has been achieved in a number of instances (see, *e.g.*, Kondo and Nakazato, *J. Pharm. Soc. Japan*, 1924, **507**, 326; Haworth and Perkin, *J.*, 1925, **127**, 1434; Haworth, Perkin, and Rankin, *ibid.*, p. 1444; Leonard and Leubner, *J. Amer. Chem. Soc.*, 1949, **71**, 3408; Clayson, *J.*, 1949, 2016), but when oxidation of a 1 : 2 : 3 : 4-tetrahydro*iso*quinoline containing a secondary nitrogen atom was attempted, only the corresponding *iso*quinolines resulted (see, *e.g.*, Schmidt, *Arch. Pharm.*, 1894, **232**, 136; 1899, **237**, 561; Buck and Perkin, *J.*, 1924, **125**, 1675; Haworth, Perkin, and Rankin, *ibid.*, p. 1686). However, by treating 1 : 2 : 3 : 4-tetrahydro*iso*quinoline with the quantity of iodine (1 mol.) necessary to remove only two atoms of hydrogen, we have obtained a mixture of tetrahydro*iso*quinoline, dihydro*iso*quinoline, and *iso*quinoline, from which the required 3 : 4-dihydro*iso*quinoline was separated *via* its picrate, albeit in low yield (20%).

McCoubrey and Mathieson (*loc. cit.*) were unable to dehydrogenate 1 : 2 : 3 : 4-tetrahydro-7-nitro*iso*quinoline under a variety of conditions. We have prepared 7-nitro*iso*quinoline in fair yield (35%) by oxidation of the tetrahydro-derivative with iodine and potassium acetate. The identity of the product was established by comparison with the 7-nitro*iso*quinoline prepared by McCoubrey and Mathieson's method and also by reduction to the known 7-amino*iso*quinoline.

Experimental.—**3 : 4-***Dihydro***isoquinoline.** To a stirred mixture of 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline (6·6 g.), freshly fused potassium acetate (5·4 g.) and boiling, dry ethyl alcohol (50 ml.), was added iodine (12·7 g.) in dry ethyl alcohol (120 ml.) during 6 hours. After 3 hours' refluxing the mixture was concentrated to small bulk, then cooled, filtered, and evaporated to dryness under reduced pressure and the brown tarry residue triturated with dilute hydrochloric acid and ether. The clear yellow, aqueous portion was made alkaline with sodium hydroxide solution, and the oil which separated was extracted with benzene. After drying (Na_2SO_4), the benzene was evaporated off, leaving a light brown oil. To a solution of this in benzene was added excess of picric acid in benzene, and the precipitated solid was once recrystallised from alcohol (yield, 9·0 g.; m. p. 163—165°). Boiling water (approx. 600 ml.) dissolved the picrates of tetra- and di-hydro*iso*quinoline, leaving that of *iso*quinoline undissolved. The insoluble residue, after repeated recrystallisation from alcohol and acetone alternately, gave a small quantity of pure *iso*quinoline picrate, m. p. 222—223°. The aqueous extract above, on cooling, gave 7 g. of mixed picrates, m. p. 165—166°, which were recrystallised from alcohol, giving 5 g. of a picrate, m. p. 171—172°. Concentration of the alcoholic mother-liquor gave crystals, m. p. 185—187°, which on repeated recrystallisation from ethanol gave pure 1 : 2 : 3 : 4-tetrahydro*iso*quinoline picrate, m. p. 199—200°. The main crop of picrate was once more recrystallised from water, giving pure 3 : 4-dihydro*iso*quinoline picrate, m. p. 175—176° (4·2 g.). This was hydrolysed with aqueous ethanolamine (Kaye, Kogon, and Burlant, *J. Amer. Chem. Soc.*, 1950, **72**, 5752), and the 3 : 4-dihydro*iso*quinoline extracted with benzene. Drying (K_2CO_3) and evaporation of the benzene gave the pure base (1·2 g.), b. p. 108—110°/12 mm.

7-*Nitro***isoquinoline.**—Iodine (33·5 g.) in dry alcohol (310 ml.) was added to 1 : 2 : 3 : 4-tetrahydro-7-nitro*iso*quinoline hydrochloride (14·0 g.; McCoubrey and Mathieson, *loc. cit.*), freshly fused potassium acetate (28·0 g.), and dry ethyl alcohol (240 ml.) under reflux, with stirring, during 5 hours. Refluxing was continued for a further 15 hours and the precipitated solid was filtered from the cooled mixture. The filtrate was evaporated to about half-bulk, a solution of concentrated hydrochloric acid (20 ml.) in water (80 ml.) added, and removal of alcohol completed under reduced pressure. The residual aqueous solution was diluted with water, filtered, and washed with ether. Addition of 20% sodium hydroxide solution until a deep orange colour just began to form, precipitated 7-nitro*iso*quinoline as a pale orange solid, which was filtered off. (If excess of alkali is added, a quantity of deep orange precipitate separates and is only removed from the product with difficulty, necessitating sublimation under reduced pressure.) The pale orange solid crystallised from light petroleum (b. p. 100—120°) as buff-coloured needles (4·0 g.), m. p. 176—177° alone or mixed with a specimen obtained by nitration and dehydrogenation of 3 : 4-dihydro*iso*quinoline (McCoubrey and Mathieson, *loc. cit.*).

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Research Division,
Allen & Hanburys Ltd., Ware, Herts. [*Received, December 30th*, 1952.]

OBITUARY NOTICE.

ARTHUR BECKET LAMB.

1880—1952.

THE present century has witnessed a vast and many-sided development of chemistry in the United States, and few are the aspects of this movement which have not profited by the life-work of Arthur Lamb.

He was born in Attleboro, Massachusetts, on February 25th, 1880, the son of Louis Jacob and Elizabeth Camerden Townsend (Becket) Lamb. During an acute illness in early childhood he was pronounced dead by the attending physician, but was afterwards revived through the persistent efforts of his mother. As a boy, he was exceptionally precocious, with a consuming interest in natural phenomena. The superintendent of schools, who had a good telescope, furthered Arthur's ambition to search for double stars. Eager to study the organisms in nearby ponds, he constructed, in the machine shop of his father's factory, quite an elaborate microscope; the lenses, only, were purchased ready made. At sixteen, already a senior in high school, his imagination was kindled by the discovery of *X*-rays, a precursor of the scientific revolution in which he was destined to have so important a part. In the same year, with a group of school friends, he produced an *X*-ray photograph, using a Crookes tube and a static machine available in the school laboratory.

As a freshman in Tufts College at Medford, Massachusetts, he planned a " major " in zoology, and spent a summer's vacation at the Marine Biological Station in Harpswell, Maine. But the vivid personality and scientific zeal of Professor Arthur Michael diverted his interest to organic chemistry. During his senior year, he undertook a research problem in that subject. In 1900, he received the bachelor's degree, and in addition the master's degree in zoology.

In September of 1902, on the eve of his departure for the Johns Hopkins University in Baltimore to continue graduate study in organic chemistry, he was persuaded to confer with Theodore William Richards of Harvard, later Nobel laureate. He was at once impressed by the possibilities of physical chemistry, then in its infancy, and so decided to devote his energies to Richards. In the laboratory of the latter, he constructed a most ingenious apparatus for precise calorimetric measurements with aqueous solutions. In 1904, he was awarded the degree of Ph.D. in organic chemistry at Tufts, and the degree of Ph.D. in physical chemistry at Harvard.

The following autumn, he went to Germany as a post-doctoral fellow. At Leipzig, Heidelberg, and Goettingen, new vistas were opened up for him by Luther, Ostwald, Bredig, and also by Haber. Some years later, his translation of Haber's classic book on the thermodynamics of technical gas reactions sharpened interest in that vitally important subject.

In the academic year 1905—6, while instructor in electrochemistry at Harvard, he was called to New York University, where he presently became a professor of chemistry and the director of the Havemeyer Laboratory. But in 1912 he returned to Harvard, this time for good.

Upon the entrance of the United States into the first world war, Lamb joined the group which was being assembled at the American University in Washington, D.C., and which later became the Chemical Warfare Service. His broad coverage of chemistry and of biology enabled him to discern the fundamental issues in a host of extremely insistent problems. Among these were the improvement of charcoal and other absorbents for gas masks and the elimination of toxic smokes. The filters devised for the latter purpose had proved inefficient and had hampered breathing, but Lamb showed that a portable electrostatic precipitator could serve much better. In Michael's laboratory he had worked on iodine pentoxide, and now with the co-operation of Charles R. Hoover of Wesleyan University he employed this substance in a device for detection of carbon monoxide. Other chemists, working under Lamb's direction, developed " Hopcalite," a catalyst for oxidation at ordinary temperatures of that same gas, then as now, a menace in tanks and in gun turrets. As the Chief of the Defence Division, with the rank of Lieutenant Colonel, he visited Europe. Later, he related with glee how as the highest-ranking officer present, he was suddenly called upon to conduct a military ceremony without the slightest advance knowledge of its intricate details.

Following the Armistice, he was summoned to organize and to direct the Fixed Nitrogen Research Laboratory in Washington, D.C. Here, in association with other leading scientists,

the reaction rates and the equilibria involved in the manufacture of synthetic ammonia were investigated, using a great variety of catalysts, and covering a wide range of temperatures and pressures. The subsequent vast expansion of this industry in the United States was based upon these fundamental studies. The Chemical Warfare Service, and also a large chemical corporation, now made tempting offers, but 1921 found him back at Harvard as a professor of chemistry and the director of its chemical laboratory.

Long before then, it had been evident that the inadequate space, bad ventilation and outmoded facilities of old Boylston Hall were strangling the teaching and the research work of the department. Lamb was active in the campaign which ultimately provided funds for the Mallinckrodt and Converse Laboratories, and he then assumed responsibility for the many technical problems involved in their construction and equipment. He had to reconcile the traditions of the architects with the ambitious demands of his own colleagues and with a shrinking dollar. As director of the new buildings, he continued to deal with human problems in addition to executive and scientific responsibilities. Presently, Radcliffe College asked him to design and supervise the construction of Byerly Hall, which had to provide, in a relatively small space, independent quarters for four different sciences.

On the educational side, also, Lamb was a commanding figure. For nearly thirty years, he conducted the large elementary course. His group of graduate students was not especially numerous, but its members were devoted to him, and quite a few of them achieved real distinction in later years. He became Erving Professor of Chemistry in 1929, and served as Dean of the Graduate School of Arts and Sciences from 1940 to 1943. He became Erving Professor Emeritus in 1948.

Space is lacking here for an adequate review of his scientific work. A part of this has been mentioned above. As early as 1913, with his student R. E. Lee, he constructed a device for comparison of densities of salt solutions by means of a magnetic float controlled by a variable electric current. In the course of this investigation, he proved that densities of water samples from various sources differed by almost one part in a million, even after elaborate purification. He thus foreshadowed the discovery of heavy water. In later years, his chief research interests were centred upon reaction rates and equilibria involving cobaltammines. With the help of research assistants, he successfully attacked many scientific problems from government organizations and from the chemical industry. He held sixteen patents, most of which had to do with his work in the Chemical Warfare Service and at the Fixed Nitrogen Research Laboratory.

Few men could have superposed upon the above-described activities the responsibilities as Editor-in-Chief of the Journal of the American Chemical Society. In his Priestley Medal Address (*Chem. Eng. News*, 1949, **27**, 2841) he has described at length the phenomenal growth of the Journal during his thirty-year incumbency, and the details of the smoothly-running organization which he developed. The volumes of this publication are his greatest monument, since adequate presentation and wide circulation of scientific data are almost as important for development of science as research itself. His standards were indeed uncompromising, and at times they irked many a prominent contributor; but they were combined with fairness, tact, and a determination to salvage everything of value in the most unpromising manuscripts. Great was his solicitude for the young and inexperienced. More than once he was seen coaching beginners in the art of scientific presentation and in literary style. Time and again, he rewrote entire articles after their authors had failed to supply adequate revisions; and through the years, each month, he shepherded authors, referees, associate editors and a secretarial staff toward the deadline—the day when the Journal went to press.

Lamb was the recipient of practically every honour which could come to an American chemist. Among learned societies should be mentioned the American Academy of Arts and Sciences, the American Philosophical Society, the Washington Academy of Sciences, and the National Academy of Sciences. He was an Honorary Fellow of the Chemical Society. Tufts conferred upon him the honorary degree of Doctor of Science in 1923. In 1933 he was elected President of the American Chemical Society. He was awarded the William H. Nichols Medal in 1943, and in 1944 the first of the Ballou Medals established for recognition of eminent Tufts alumni. Most coveted of such distinctions is the Priestley Medal of the American Chemical Society, which came to him in 1949.

Lamb's friends will always think of him first as a human being. He was an enthusiastic tennis player, and during summer vacations he hiked and climbed in Switzerland, the Tyrol, or the Canadian Rockies. He was a member of the exclusive American Alpine Club. In Brookline, where he lived for many years, he was a trustee of its public library and active in the work of the Boy Scouts. But it was in his home that loyalty and devotion reached their fullest

stature. In 1923, he married Miss Blanche Anne Driscoll, a lady of great artistic ability, and of rare courage in the face of agonizing physical ailments which beset her in later years. Their two children, David Becket and Deborah Anne, survive them.

Throughout his brilliant career, everyone marvelled at Lamb's prodigious energy, but in 1947 came the sudden realization that his heart had been overtaxed. Warnings disregarded, he was enabled by expert medical advice and an equable disposition to continue on a crowded schedule for five years more. In September, 1951, after his attendance at two scientific meetings, his malady was aggravated. He died suddenly on May 15th, 1952, while riding homeward at the end of a busy day.

G. S. Forbes.

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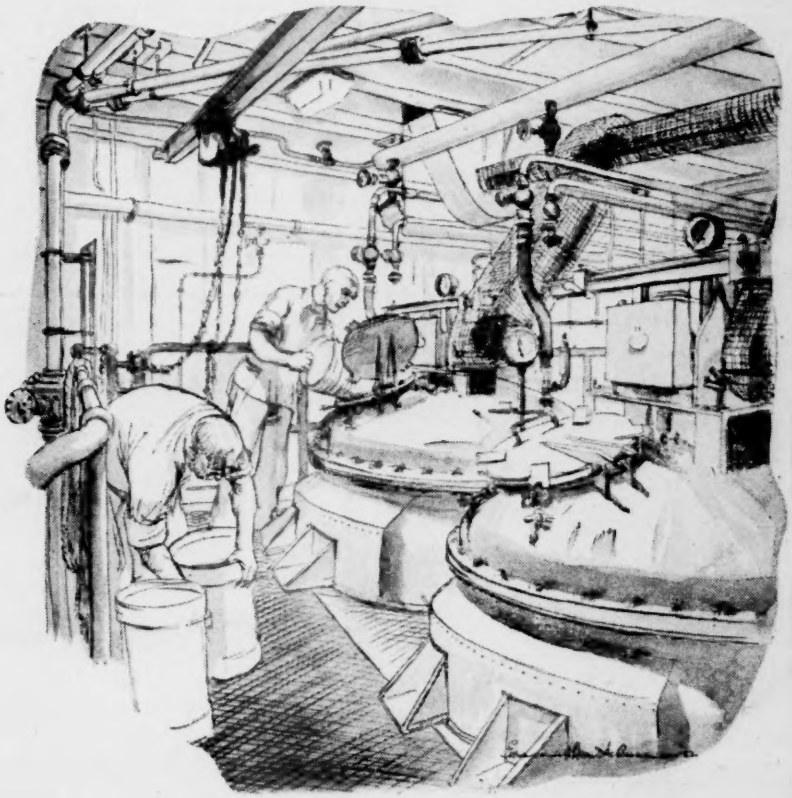

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